

The American Journal of Medicine

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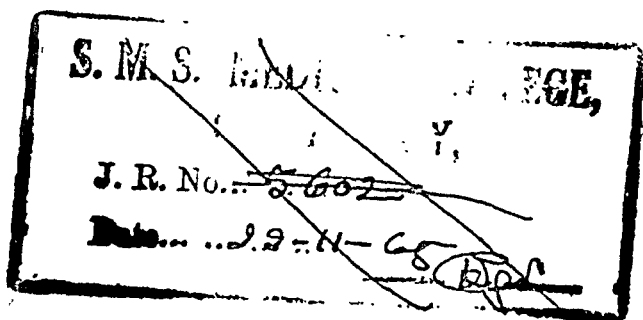
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Editorial

Retrospect and Prospect

THIS issue initiates the second year of publication of The American Journal of Medicine. The occasion would seem appropriate for a review and assessment of what has been accomplished and for a statement of the program and plans for the coming year.

As set forth in the introductory editorial outlining the objectives of The American Journal of Medicine (July, 1946), it was hoped that the new journal would serve two useful and creditable functions: To add to the available media for publication of the results of sound clinical investigation; and to make more effective use of the teaching opportunities of the medical periodical as an instrument for instruction at a post-graduate level. To realize this dual aim it was proposed to combine reports of original clinical research and case studies with conferences, reviews, seminars and symposia designed chiefly for integrated teaching. By thus reflecting both the research and teaching programs of our large medical schools and clinics it was hoped to present a fairly representative cross section of current medical activities for those interested in keeping abreast of developments.

With regard to papers dealing with original investigation, it has been the policy of The American Journal of Medicine to seek a middle road between highly specialized research of immediate interest to very few and repetitious accounts of clinical experiences already familiar to most. There

has been no difficulty in obtaining experimental and clinical studies of high caliber and of the desired character and scope; in fact, the influx of deserving manuscripts has been so great as to overtax the capacity of the Journal. It would appear that the Journal is already filling a real need in making available these additional facilities for publication of the results of responsible clinical investigation.

With regard to the extensive teaching program of The American Journal of Medicine, an effort has been made to choose forms of exposition that will interest and stimulate. The Conferences largely employ the time-tried Socratic method for enhancing and sustaining interest and have proved especially effective media. The Cornell Conferences on Therapy deal informatively yet informally with problems in the theory and practice of therapeutics. The topics selected are timely, the discussions are comprehensive and veered to include considerations often neglected in textbooks but which turn up (or should turn up) frequently in practice. The Columbia Combined Staff Clinics have attracted attention as an interesting development in the evolution of the clinic. Problems of disease are introduced with an extensive analysis of the basic mechanisms involved, then constructively correlated with diagnostic and therapeutic considerations to form a well rounded whole. The Washington University Clinico-pathological

Conferences have proved to be model exercises of their kind, focusing on the significance and interpretation of clinical and laboratory data rather than on statistical probabilities, yet maintaining the element of suspense. The pathological dénouement especially emphasizes such findings as might throw light upon the mechanisms of the disease under consideration.

Two interesting and instructive series of seminars have appeared, one on the therapeutic use of antibiotics, the other on rheumatic fever. A recent issue (May, 1947) contained the Journal's first symposium, a comprehensive presentation of current views on streptomycin and its therapeutic applications. Reviews and editorials summarizing a variety of appropriate subjects have been published in each issue. For all these, the seminars, symposia, reviews and editorials, it has been possible to enlist the cooperation of authoritative contributors who have given generously of their time to aid the teaching program of the Journal.

These efforts appear to have met with an appreciative response. That The American Journal of Medicine has won such wide acceptance in its first year of publication is most gratifying to the Editorial Board and to the publishers, and is taken to be an acknowledgment of the need for a journal of this kind and an endorsement of the general policies adopted. It is accordingly proposed to continue along the lines already laid down, preserving sufficient flexibility to introduce such modifications as may be indicated. The high standards in content and format will be maintained.

The program for the coming year includes a number of stimulating reports of clinical research utilizing metabolic and bacteriological technics. Controlled studies on new drugs of clinical significance will be

given appropriate emphasis, one such appearing in this issue. A number of meritorious case reports are also on hand. Arrangements have been made for the continued appearance of the Conferences, which will be scheduled as in the past, the Cornell Conferences on Therapy alternating with the Columbia Combined Staff Clinics, the Washington University Clinico-pathological Conferences appearing each month.

The subjects selected for treatment as seminars (integrated series of articles appearing in six successive issues) are thromboembolism, beginning with the introductory article in this issue; and hypertension, beginning January 1948. These are timely and many-faceted topics which will be discussed from different points of view in an attempt to arrive at some clarification of their present status, particularly as to therapeutic policy. The contributors are especially qualified investigators long identified with the problems under discussion.

Another comprehensive symposium, this one on allergy under the combined guest editorships of Dr. Robert A. Cooke and Dr. Francis M. Rackemann, will appear in the fall. The symposium has been especially designed for a general medical audience. Reviews will appear in each issue, preference being given to those showing critique and constructive interpretation. A new department, "Letters to the Editor," is contemplated if there is sufficient demand; this may be utilized for brief comment on articles which have already appeared, or for early publication of abbreviated original communications.

Such are the plans for the coming year. To make possible their realization, The American Journal of Medicine looks to its many friends for continued loyal support.

ALEXANDER B. GUTMAN, M.D.

The Influence of Dibenamine (N, N-Dibenzyl- β -Chloroethyl-Amine) on Certain Functions of the Sympathetic Nervous System in Man*

HANS H. HECHT, M.D. and ROSCOE B. ANDERSON, M.D.

SALT LAKE CITY, UTAH

A SERIES of tertiary amines, structurally related to nitrogen mustards (bis- and tris-chloroethyl amines), has been recently introduced with the claim that compounds of this type block or reverse certain excitatory adrenergic responses in a variety of animals. These agents were found to be only moderately toxic and were effective when administered by mouth or vein, subcutaneously or intraperitoneally.¹ At least one chlorine and one benzyl group was found to be necessary for activity. (Fig. 1.)

One of these compounds, dibenzyl- β -chloroethyl amine ("dibenamine") was made available to us for clinical trial and has been administered as its hydrochloride salt to fifty-four patients.†

DOSAGE AND ADMINISTRATION

Mono-chloroethyl amines are less irritant than bis- and tris-compounds (nitrogen mustards) but local irritation and tissue necrosis have been observed in animals following the administration of dibenamine and for this reason subcutaneous and intramuscular injections were avoided and no rectal suppositories were made. The com-

pound was administered by mouth to twenty-two patients. Gelatine capsules containing 100 and 200 mg. dibenamine hydrochloride in lactose were administered with meals twice or three times daily for as long as six weeks, in doses ranging from 200 mg. to 1 Gm. per day (average 400 mg per day). Nausea, vomiting and burning in the epigastric region occurred frequently. Oral administration was abandoned when it became apparent that the pharmacologic effects in doses which could be tolerated were inconstant and unpredictable when given alone or in conjunction with parenterally administered dibenamine solutions.

Intravenous administration was found to be the only route which was safe and which gave consistent and predictable results. The effective dose which can be tolerated appears to be 4 to 6 mg./Kg. body weight (0.25 to 0.50 Gm. per patient). This was administered as a 10 per cent solution in propylene glycol or in 50 per cent acid alcohol, but it was further diluted immediately before administration to at least 50 ml. when it was given by slow injection or to 300 ml. when given by infusion. The infusion method was preferred because leakage from the vein or paravenous injection may

† Dibenamine was supplied by Givaudan-Delawanna, Inc., New York, N. Y.

* From the Department of Medicine of the University of Utah School of Medicine. Part of this investigation was supported by grants from the Fluid Research Fund of the Rockefeller Foundation, the Utah Copper Company Research Fund and the Physicians Research Fund of the University of Utah. Read, in part, at the Meeting of the Western Society for Clinical Research, San Francisco, Calif., November 1, 1946.

cause severe local reactions and since rapid intravenous injections have caused coordinated clonic convulsions in animals. As will be shown below, there is evidence that dibenamine may initiate convulsive seizures in man. Larger doses comparable to those

oscillometric indices and on alterations in sweating. Some of the undesirable reactions which occurred during the resting phase following the injection may be regarded as further evidence of an altered autonomic balance.

The second group tested the activity of the sympathetic nervous system on exercise. This was accomplished by recording the changes in arterial blood pressure upon changes in posture, upon breathing a low concentration of oxygen or carbon dioxide, upon submerging one extremity in ice water and upon breath-holding. Postural changes were checked against the "Flack test" during which the subject blows against the mercury column of a sphygmomanometer kept at 20 to 30 mm. pressure.

The third group of tests consisted of direct stimulation of the sympathetic nervous system by the injection of sympathomimetic compounds. Two were selected for trial: one was epinephrine, given intravenously in doses of 50 to 100 micrograms by syringe, or intramuscularly in doses of 10 micrograms per Kg. body weight. Before, during and after the injections, arterial and venous blood pressures, skin temperatures, heart rates and electrocardiograms were recorded and the results were analyzed and tabulated. Capillary blood sugar determinations were performed following an intramuscular injection of epinephrine. All procedures were repeated in the same subject at various intervals following an infusion of dibenamine. Neosynephrin hydrochloride was selected as a second sympathomimetic compound because, in contrast to epinephrine, its action appears to be one of peripheral vasoconstriction without appreciable direct cardiac stimulation. One mg. of neosynephrine was injected by syringe and the same procedures were carried out that were used to evaluate the epinephrine response.

It was thought that these three groups of tests performed on the same patient before

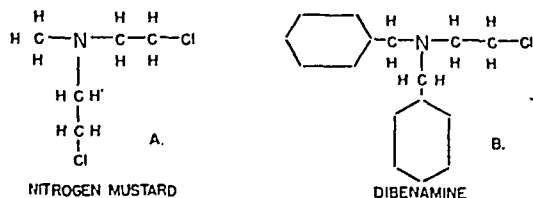


FIG. 1. A, structural formula for methyl-bis- β -chloroethyl-amine, a nitrogen mustard. B, formula for dibenzyl- β -chloroethyl amine: "Dibenamine." The structural similarity of the two compounds is apparent. The nitrogen mustards owe their physiologic activity to an intramolecular ring formation with liberation of Cl.² A similar mode of action has been proposed for dibenamine.¹

used in animals (10 to 20 mg./Kg.) were not tolerated.

MATERIAL AND METHODS

Thirty-six patients received a total of sixty-two injections of dibenamine. Ten patients received repeated doses; in two of these, daily injections were given for six consecutive days. Toxic reactions were recorded and thirty of these patients were studied for evidence of alterations in the activity of the sympathetic nervous system. This was gauged by a number of tests which were expected to yield information on the activity of the adrenergic system at rest and during stress.

The tests may be divided into three groups. The first included those which were thought to give evidence of a blockage of the sympathetic nervous system at rest. This required observations on the reaction of the pupils to light, on changes in the temperature of the skin during and following the injection, on alterations of arterial blood pressure as an indication of a change in the resting arteriolar tone, on changes in the

and at regular intervals after the administration of dibenamine would allow some insight into the action of this drug in man, and that the results obtained would furnish a basis for further clinical studies.

Of the thirty patients thus tested, six were suffering from essential hypertension, four from "renal" hypertension (two chronic glomerulonephritis, two intercapillary glomerulosclerosis), four had evidence of heart disease with and without cardiac irregularities, seven suffered from peripheral vascular diseases and ten were considered as normal for the purpose of this study.

TOXIC EFFECTS

Reactions to the injection of dibenamine were frequent. Their heterogenous character may be explained by (1) the irritating nature of the drug administered (venospasm and phlebothrombosis); (2) its generally toxic effects (nausea, psychosis and convulsions) and (3) by vasodilatation (congestion of nasal mucosa and tingling of the feet). The last effects apparently result from the temporary removal of a sympathetically maintained vasomotor tone. This must be viewed as a primary action of an agent supposedly interfering with autonomic control and may not necessarily represent toxic reactions or a side effect. The same might be said for some of the reactions listed under toxic effects. These might be taken as the effects of a blockage of certain autonomic functions of the central nervous system which are at present incompletely understood. The lack of information which exists in regard to the humero-nervous regulation of many vegetative functions makes the exact evaluation of the site of action of a "sympatholytic" agent almost impossible and has prompted the listing under this heading of all effects not looked for specifically.

Such "side reactions" were always disagreeable and occurred in twenty of the

thirty patients tested (67 per cent) or thirty-three times following fifty-one injections (65 per cent). Nausea with and without vomiting was frequent (twelve times in eight patients). Excessive drowsiness and dizziness were common (nine times in eight patients). Sweating, nasal congestion and tingling of the feet were noted nine times in six patients; restlessness, irritation and palpitation eight times in four patients; pain along the arms during the infusion four times in four patients and thrombophlebitis once. Mental confusion with a peculiar disturbance of time sensation, hallucinations and perseverations lasting for several hours and with full insight into the abnormal mental state during the reaction and afterwards were noted in four patients (13 per cent), but may have occurred more frequently as some of the patients appeared reluctant to recount their experiences. Once a severe convulsive seizure was noted, followed by a postconvulsive stupor lasting for several hours. The patient, who suffered from multiple sclerosis, insisted upon another injection because he "felt greatly improved." Another injection containing one-half of the original dose (5 mg./Kg.) was given two months after the first infusion; another seizure occurred but was less severe. No lasting effects were noted in any patient. No striking alterations occurred in bodily functions, including bowel habits and no changes were noted in temperature, electrocardiograms, blood counts or urinalyses.

CERTAIN EFFECTS ON THE RESTING INDIVIDUAL

A slight reduction in systolic and diastolic arterial blood pressure over the resting pre-injection value was noted seven times in twenty-seven patients. Two of these patients had resting values above the normal range. The reduction in pressure was not striking; it had disappeared within twelve hours in all but two cases. It was thought unlikely

that prolonged bed rest was the cause of these changes as these effects were transient and pre-injection values were reached within a day after the infusion had been given.

Visible peripheral vascular dilatation with flushing of the extremities was not

counted for differences in measured temperatures caused by increased heat removal. (Fig. 2.)

In all patients the pupils became constricted during the infusion and became fixed within about two hours after the in-

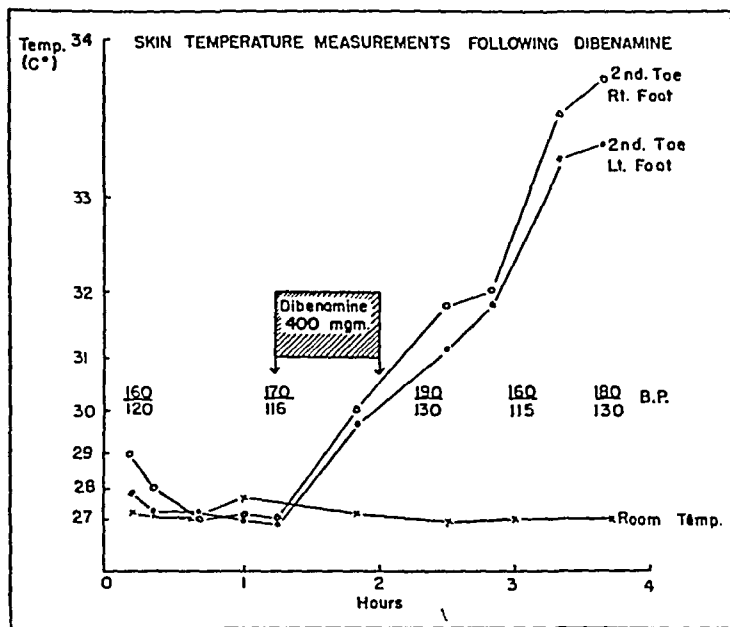


FIG. 2. Temperature measurements on two toes before, during and after a dibenamine infusion given to a male patient, thirty-five years of age, with severe essential hypertension. The patient was resting without covers in a warm room. Note the absence of blood pressure changes in spite of a rising skin temperature. The patient developed a pronounced orthostatic hypotension at the end of the test period.

common but was noted occasionally. In nine patients skin temperature measurements were performed over the distal points on upper and lower extremities at regular intervals before, during and after infusion of dibenamine. A significant increase in skin temperature was noted in four cases, all instances of peripheral vascular diseases (hypertension, thromboangiitis and Raynaud's syndrome). The changes observed were temporary, but it was considered that the measurements indicated an increase in peripheral blood flow because the temperature and humidity of the room were kept relatively constant and no alteration in sweating occurred which could have ac-

fusion was terminated. This was a constant and long-lasting effect which gradually abated and usually disappeared by the end of the first week. The effect upon the pupils was so constant and occurred so regularly with such small doses that it was used as an indication that the agent had acted in the resting patient. No pupillary response was noted in one patient with acute glaucoma. A slight tachycardia was usually noted for several hours following the injection.

VASCULAR RESPONSE DURING EXERCISE

When the patients rose from the supine position, a striking fall in systolic and diastolic pressures was noted in subjects

with normal blood pressure as well as in hypertensive individuals. This was commonly accompanied by dizziness and fainting and in one instance resulted in a brief convulsive seizure. As soon as the patients reclined, all symptoms disappeared and the

only four were no significant changes observed (intercapillary glomerulosclerosis, Raynaud's syndrome and multiple sclerosis with extreme spasticity of the lower extremities). A precipitous drop in blood pressure was prevented by applying large

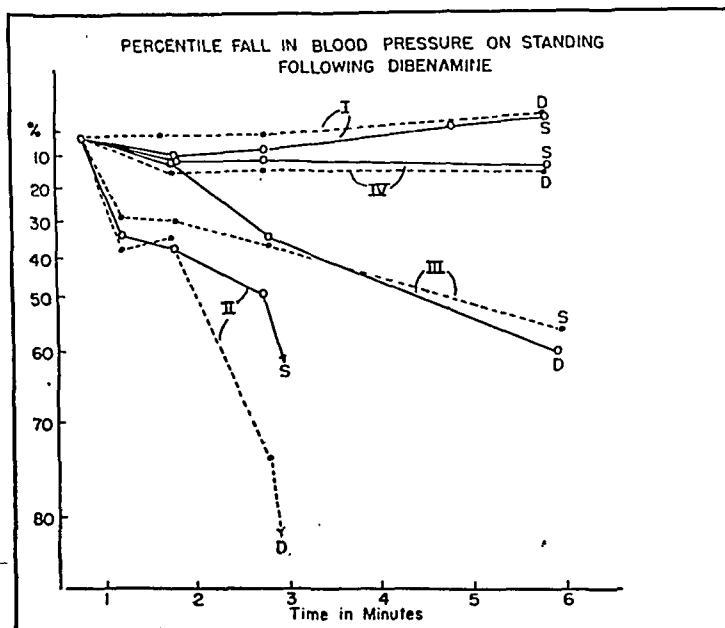


FIG. 3. Orthostatic hypotension of brief duration following a dibenamine infusion in a male patient, forty-two years of age, with severe hypertension and obliterative endarteritis. At the end of the infusion the patient fainted after standing erect for three minutes. Diastolic pressure was unobtainable at this time. i. Blood pressure before dibenamine; ii. at end of infusion; iii. two hours later; iv. twenty-four hours later. The changes are expressed in per cent, in relation to original blood pressure levels. s, systolic blood pressure readings; d, diastolic blood pressure readings.

arterial pressure returned to its previous level. The orthostatic hypotension thus produced was usually maximal within six hours, noticeable for one or two days and occasionally lasted longer. (Fig. 3.) In one instance, that of a far advanced case of chronic glomerulonephritis, orthostatic hypotension was noted for nine days following a single injection. In this patient no fall in blood pressure occurred on several occasions before dibenamine was administered and the hypotensive effect gradually diminished during the second week. Postural changes were tested in eighteen patients and in

abdominal binders, by wrapping the lower extremities in elastic bandages or by a combination of both. (Fig. 4.)

Fall of arterial pressure upon standing may be explained in part by a loss of sensitivity of the carotid sinus.³ It is primarily, however, a consequence of the diminished cardiac output which follows incomplete cardiac filling. This, in turn, is apparently caused by failure of postural venous constriction necessary to overcome the hydrostatic pressure within the vascular system.⁴ It may be considered an instance of true forward failure with venous pooling, ap-

parently the result of an alteration of the peripheral (venous) vascular tone. This can be tested in the resting patient by raising intrathoracic pressure and substituting this for the increase in hydrostatic pressure. The intrathoracic pressure is raised by exhaling

existed. This patient had to exert considerable muscular effort to balance herself upon standing. This may have influenced the results obtained through compensation for venous relaxation by increased muscular exertion. With the patient relaxed, a signi-

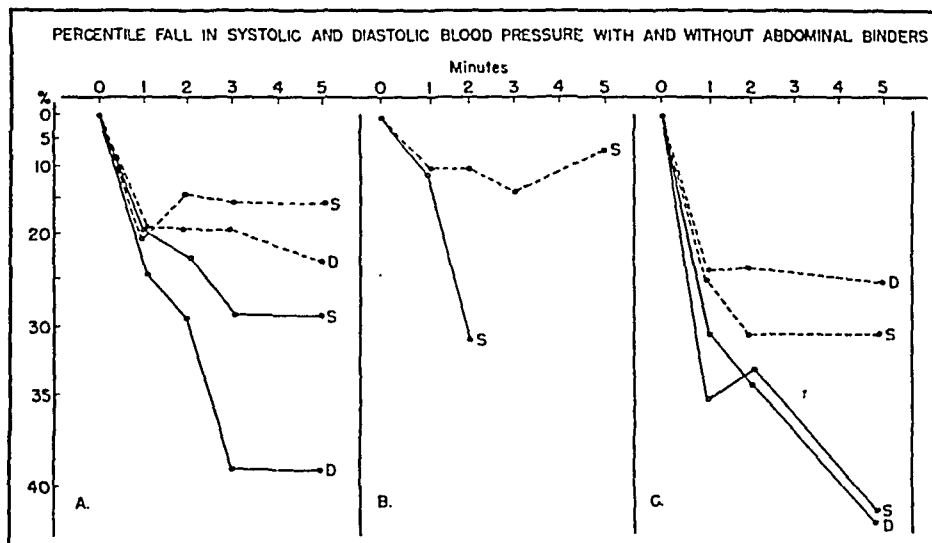


FIG. 4. Orthostatic hypotension following dibenamine infusion in three patients: A, chronic glomerulonephritis; B, essential hypertension; C, obliterative endarteritis; abdominal binders reduced the severity of the reactions. o—o systolic and ●—● diastolic pressure; — without and - - - with abdominal binders.

against a fixed resistance, which causes pronounced hypotension in susceptible individuals. It is the basis for the so-called Flack test which requires the patient to blow against the column of a sphygmomanometer at 20 to 30 mm. Hg pressure for 20 seconds.^{4,5} A positive Flack test, indicated by a fall in arterial systolic and diastolic pressures, was always present in this series when orthostatic hypotension was noted. If for certain reasons the patient was unable to stand, a positive Flack test could be used as an indication that reflex venous constriction had been blocked. Repeated Flack tests were performed on sixteen patients, fourteen of whom were also tested for orthostatic hypotension. A negative Flack test was observed in four instances. The only discrepancy between the two tests was noted in a case of multiple sclerosis, in which spasticity of the lower extremities

significant fall in pressures occurred during the Flack test.

Arterial blood pressures will rise in response to various stimuli⁶ which are largely based on reflex vasoconstriction mediated through the vasomotor centers. In the present series changes in blood pressure readings were recorded following inhalation of 10 or 12 per cent oxygen or carbon dioxide, after the patient had held his breath for 20 seconds and during and after submerging one extremity in ice water. The blood pressure response to anoxia and to inhalation of carbon dioxide was usually much less striking than that following breath-holding or subsequent to the "cold pressor test." Only the results of the latter two tests will be discussed. In the breath-holding test the patient was instructed to hold his breath for 20 seconds without forceful in- or exhalation preceding the arrest of breathing and without closure

of the glottis during the test.⁷ In the eleven patients who were subjected to this procedure, no satisfactory rise was noted in six. The response in the other five individuals could be completely suppressed by administration of dibenamine, and in two individuals a slight fall in pressure was noted instead of the expected rise. The cold

cold pressor effect in the face of a reversal of the breath-holding test and a markedly positive Flack test lasting for three days.

RESPONSE TO INJECTED SYMPATHOMIMETIC COMPOUNDS

Intravenous Administration of Neosynephrin.

Previous observations have shown that the

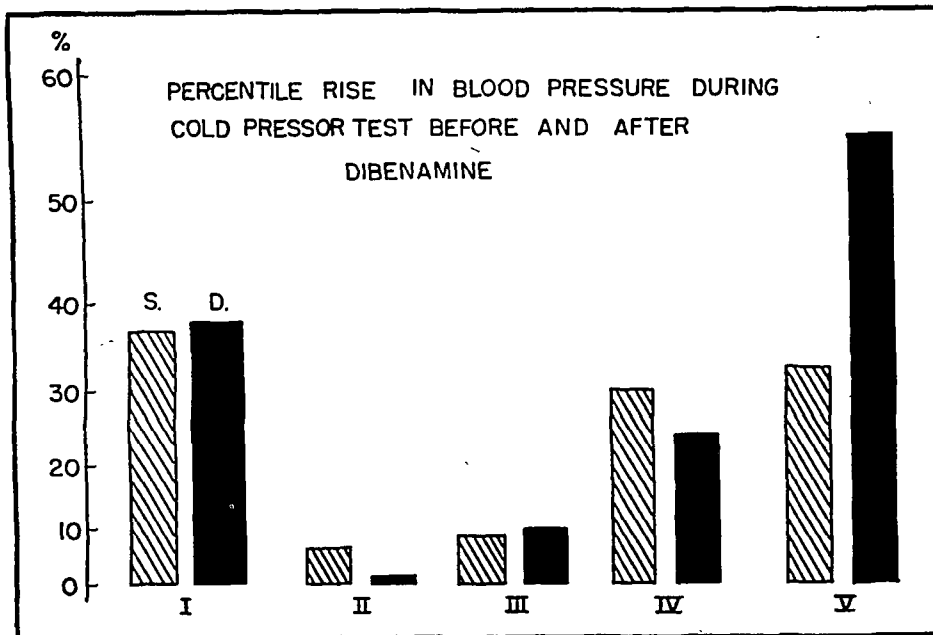


FIG. 5. Blocking of the usual reflex rise in blood pressure upon submerging one extremity in iced water for one minute (Hines' cold pressor test.)⁸ The blocking effect of dibenamine was seen to last for at least two days in this forty-six year old female patient with essential hypertension and hypertensive heart disease. I. Before dibenamine; II. two hours after infusion; III, IV and V. one, two and four days, respectively, after the end of the infusion. The columns represent the percentage increase in blood pressure at one minute after onset of test. (Later values showed no qualitative differences.) S, systolic blood pressure reading; D, diastolic blood pressure reading.

pressor test⁸ was performed on seventeen individuals and a significant rise in pressure was noted in fifteen. Of these, a blocking of the expected response was observed in eleven individuals. No appreciable effect was noted in four (chronic glomerulonephritis, intercapillary glomerulosclerosis, achlorhydria and essential hypertension); even so a profound hypotensive effect upon change in posture could be elicited in all the subjects. Figure 5 shows the blocking effect observed in one example and Figure 6 illustrates the failure of dibenamine to block the

intravenous administration of this and similar compounds (paredrinol and paredrine) to normal subjects is regularly followed by a number of predictable changes; namely, a rise in systolic, diastolic and venous pressures, pounding and palpitation of the heart and excessive slowing of the heart beat.⁹ A more recent analysis¹⁰ of the changes which occur has revealed that the rise in peripheral pressure can be prevented or interrupted by vasodilator substances and that the changes in heart rate can be blocked by the administration of atropine. The

bradycardia is caused by reflex vagal slowing secondary to the rise in intravascular pressures. In man, suppression of the sinus node is followed by a variety of escape phenomena with the occurrence of auriculo-ventricular nodal rhythms and A.V. dissociation.

dividuals and cause few of the cardio-excitatory effects of epinephrine itself.

One mg. of neosynephrin was administered by vein to nine individuals and partial or complete blocking of all these effects was readily obtained. Doses as high as 5

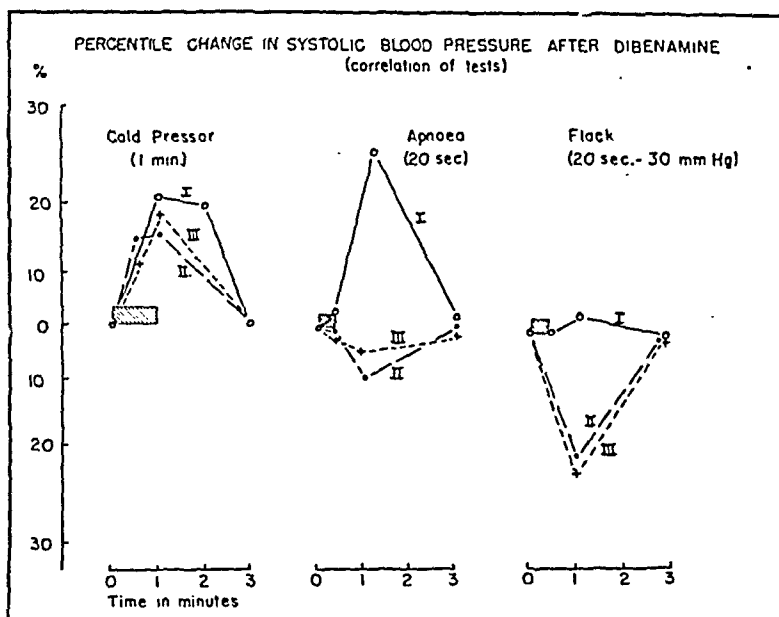


FIG. 6. A correlation of tests in a sixty-nine year old patient with portal thrombosis and a presumably normal cardiovascular system. The chart reveals that the blood pressure response to breath holding and to blowing against fixed resistance (Flack's test) was prevented by one infusion of dibenamine for at least three days, but that the cold pressor response remained essentially unaltered. Only systolic pressures are charted. I, Before dibenamine; II and III, eighteen and sixty-eight hours, respectively, after the end of the infusion.

tions with and without interference and fusion beats. Prolongation of A.V. conduction is frequently seen and may be interpreted as the negative dromotropic effect of excessive vagal stimulation. Certain changes in the configuration of the ventricular deflection of the electrocardiogram are likewise explained as being secondary to vagal action. Many of these changes are peculiar to man and have been used for the experimental production of nodal rhythms and other irregularities in normal and abnormal subjects.¹⁰ Sympathomimetic compounds of this kind appear to possess a predominant peripheral action in most in-

mg. intravenously were tolerated without any appreciable changes occurring in arterial pressure, venous pressure or in the heart rate. A summary of the changes observed after the injection of one mg. under the influence of dibenamine is given in Table I.

Intravenous Administration of Epinephrine. The reactions following the rapid intravenous administration of small amounts of epinephrine are far more complex and quantitatively more pronounced than those observed following the injection of other sympathomimetic compounds. Briefly, the following changes can be observed when

100 micrograms (1 to 5 microgram/Kg.) are injected undiluted intravenously: Within

TABLE I
PERCENTILE CHANGES OF CERTAIN VASCULAR RESPONSES
TO THE INTRAVENOUS ADMINISTRATION OF 1 MG. NEO-
SYNEPHRIN BEFORE AND AFTER DIBENAMINE HYDRO-
CHLORIDE (NINE PATIENTS). THE OBSERVATIONS
WERE CARRIED OUT FOR TEN MINUTES

Findings	Percentage Change	
	Before	After
	Dibenamine	
Average rise in systolic pressure...	25.7	3.4
Average rise in diastolic pressure...	24.5	3.0
Average rise in venous pressure (five patients).....	43.7	14.5
Average decrease in heart rate....	30.6	2.5
Incidence of abnormal cardiac rhythm by "sinus default".....	33.3	0.0

10 to 20 seconds, systolic, diastolic and venous pressures rise steeply, hyperventila-

tion sets in (occasionally preceded by a short period of apnea) and the patient develops a deathly pale color due to constriction of the skin capillaries. At times pain over the lower back is experienced, severe palpitation is noted and vascular sounds and heart sounds increase in intensity. The heart rate may at first slow down in response to a vagal reflex, but it soon increases and many ectopic foci awaken and generally assume control of the heart for 1 or 2 minutes. Paroxysmal ventricular tachycardia arising from various foci and occasionally alternating in type (bidirectional) is frequent. When the effect of epinephrine on the ventricular muscle begins to wear off, auricular paroxysmal tachycardia becomes noticeable, occasionally in association with A.V. block. Although the effect has usually passed off within a few minutes, the disagreeable subjective sensations and the objective findings make this an undesirable experience both for the subject and the examiner. When an

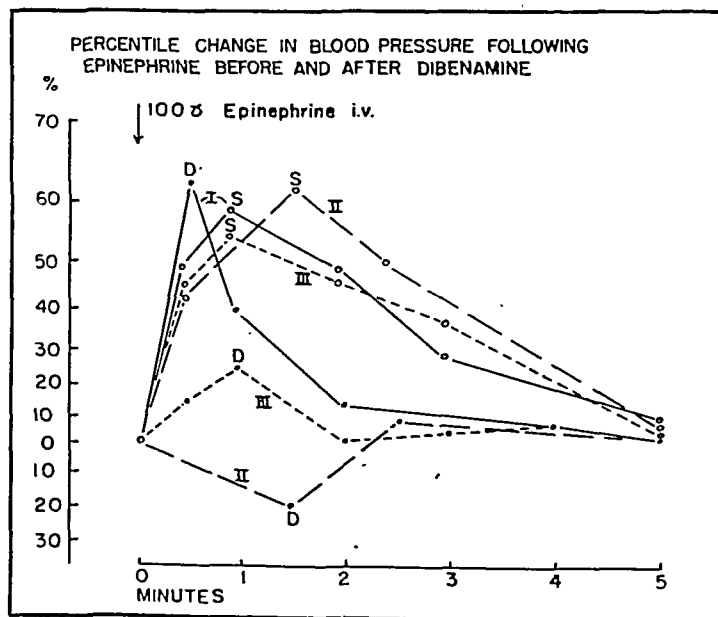


FIG. 7. The response of systolic and diastolic blood pressure to 100 micrograms epinephrine injected intravenously before and at various intervals following a dibenamine infusion (patient in Figure 6). Note that in this instance the effects of dibenamine are confined to the diastolic pressure. I, Before dibenamine; II, five hours; III, four days after an infusion of dibenamine. S, systolic pressure; D, diastolic pressure.

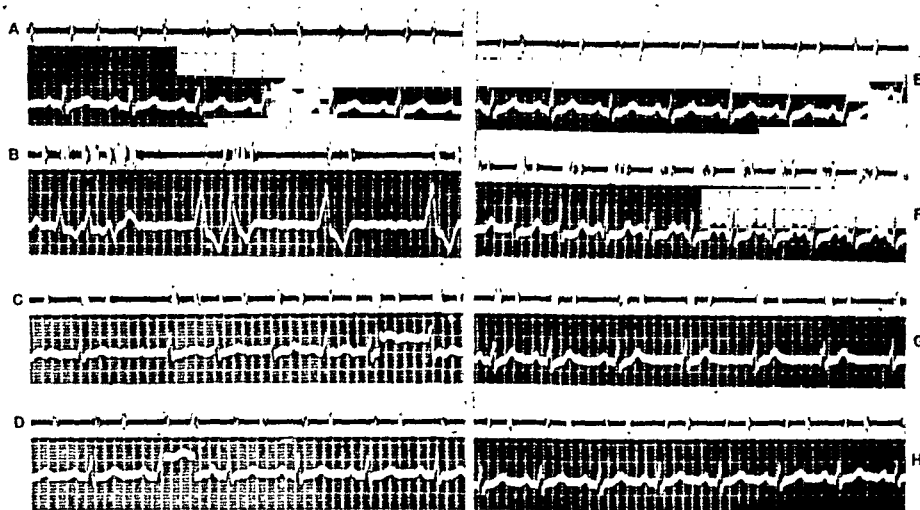


FIG. 8. Phonocardiograms from the apex and lead II of the electrocardiogram in a patient not included in this series. A and E are control records. E, two hours after an infusion of dibenamine; B and F, C and G, D and H, one, two and five minutes after the intravenous injection of 100 micrograms of epinephrine hydrochloride. In B and C a paroxysm of auricular fibrillation is seen, apparently induced by epinephrine. In B the heart is driven entirely by ectopic foci. The increase in the intensity of the first and second heart sounds and the presence of a systolic murmur may be taken as indirect indications of increased cardiac output and an increased speed of blood flow. Following dibenamine, only minor cardiac irregularities are noted (by "sinus default" due to slight increase in systolic pressure). The ventricular complexes of the electrocardiogram reveal S-T depression and in F a marked prolongation of the Q-T interval is noted. The end of the second heart sound now coincides with the rising limb of T in contrast to the usual findings seen in E and H where the end of T coincides with the end of the second sound. Note the increase in the intensity of the first and second sounds and the occurrence of a systolic murmur as before (cardiac output and circulation times unaltered by dibenamine).

attempt was made to ameliorate the effects by lowering the dose of injected epinephrine, it was noted that some of the excitatory effects did not occur and that the response more closely resembled that usually seen with neosynephrin. One hundred micrograms must therefore be given if the effects of epinephrine on the heart as well as on the peripheral vascular system are to be investigated.

The response to epinephrine given intravenously before and after the administration of dibenamine was tested in ten subjects. Following dibenamine the response was modified but was never completely blocked. The subjective sensations of the patient remained unaltered although they were less

severe; hyperventilation, constriction with extreme paleness of the skin remained unchanged, the increase in intensity of the heart sounds as well as pounding and palpitation of the heart was observed and appeared similar to that experienced prior to dibenamine administration. The systolic pressure rose slightly while the diastolic pressure fell abruptly, resulting in an increase in pulse pressure over the resting values. (Fig. 7.) A fall in blood pressure following the administration of epinephrine, commonly seen in animals under the influence of various sympatholytic compounds, including dibenamine, was observed only once in an individual suffering from arteriosclerotic heart disease. In response to

epinephrine the patient developed paroxysmal tachycardia before and after dibenamine administration. A reduction of cardiac output occurred each time but was compensated by an epinephrine-induced peripheral vascular constriction before, but

normal heart beats, as seen in the electrocardiogram, could be observed which had been obscured by the striking irregularities present before. (Fig. 8.) Thus, a depression of the S-T segment with flattening of T previously described following the intra-

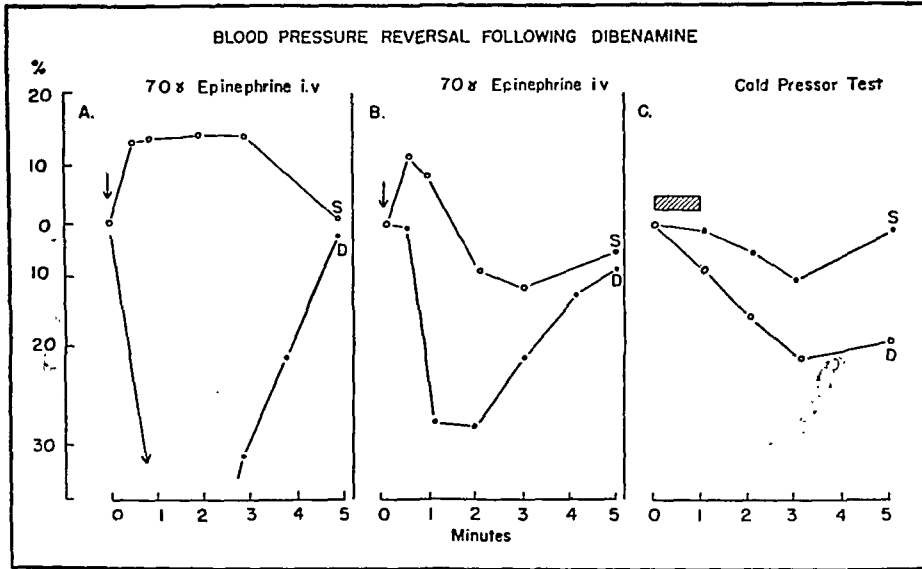


FIG. 9. "Epinephrine reversal" following dibenamine administration. A and B demonstrate a slight rise in systolic and a fall in diastolic pressures following intravenously administered epinephrine in patients previously given dibenamine. In B, a secondary fall in systolic pressure is seen. The response is similar to that seen after subcutaneous administration of epinephrine. C illustrates complete reversal of the usual blood pressure response to the "cold-pressor test." It is assumed that only the excitatory component of epinephrine (sympathin E) is blocked and that the reactions illustrated are based largely on the effects of "sympathin I," the inhibitory component.

not after, dibenamine was given. Other examples of "partial" blood pressure reversal are shown in Figure 9. In all the subjects the heart rate increased following epinephrine and the administration of dibenamine, but the incidence of epinephrine-induced ectopic ventricular beats decreased considerably. When the one case cited above is excluded, the incidence of abnormal ventricular beats after the injection of epinephrine during one minute of continuous recording dropped from thirty-seven to one when dibenamine had been given. A summary of these findings is given in Table II.

When blocking had occurred, certain changes in the ventricular complexes of the

muscular or subcutaneous administration of epinephrine was now noted in all instances. In addition, all subjects revealed a relative prolongation of the Q-T interval (electrical systole). This appears to be a hitherto unrecognized but typical response to epinephrine which can be noted from published tables¹² and tracings.¹³ In animal experiments^{14,15} epinephrine shortens the mechanical systole. In man a true prolongation of the Q-T interval is present above the predicted normal, and the changes illustrated cannot be construed as indicating a shortening of the mechanical with a normal electrical systole because a true prolongation of the Q-T segment was present above the predicted normal. In this respect the disso-

ciation of the two events in the cardiac cycle is similar to those previously noted in hypocalcemia.¹⁶

Many of the effects of epinephrine appear uninfluenced by dibenamine. The present evidence indicates that cardiac output and peripheral blood flow, respiratory volume, certain effects on the capillary system and the rise in blood sugar which follow the administration of epinephrine are little influenced if preceded by the injection of dibenamine. In fact, the absence of epinephrine-induced vasoconstriction at the injection site resulted in a steeper and higher rise of blood glucose in response to epinephrine given intramuscularly after dibenamine was administered than was observed in the same individual before.

COMMENTS

The testing of allegedly sympatholytic compounds in man is fraught with difficulties because many of the actions of the sympathetic system and the mechanisms by which they are produced have not been elucidated completely. The injection of epinephrine and related compounds cannot be considered to be a completely satisfactory mode of duplicating what happens in the intact human body upon excitation of the adrenergic system. In the present report only a few of the known mechanisms occurring spontaneously or upon the injection of such compounds have been tested. Care was taken in all instances to have the patients serve as their own controls, thus eliminating the many individual differences in response which may be obtained upon the administration of epinephrine and like substances. In this report special emphasis has been placed on the alterations occurring in the cardiovascular system because these lend themselves to simple and clear-cut experiments and the vascular system reacts so readily to small doses of epinephrine; also its response to adrenergic stimuli can be

blocked easily. A tentative summary of the alterations which may be induced by dibenamine upon a number of autonomic functions is given in Table III.

No attempt is made to correlate these findings with the results observed by others

TABLE II
PERCENTILE CHANGE OF CERTAIN VASCULAR RESPONSES TO
THE INTRAVENOUS ADMINISTRATION OF 50 TO 100
MICROGRAMS OF EPINEPHRINE BEFORE AND AFTER
DIBENAMINE HYDROCHLORIDE (TEN PATIENTS)

Findings	Percentage Change	
	Before	After
	Dibenamine	
Average rise in systolic pressure during five minute period after injection	26.5	11.7
Average change in diastolic pressure during five minute period after injection	7.8	-22.9
Average increase in pulse pressure during five minute period after injection	48.0	70.0
Average increase in heart rate during five minute period after injection	4.7*	28.3
Number of abnormal ventricular beats during first minute period after injection	37	1

* The heart rate decreased temporarily in five of ten cases (secondary vagal stimulation). A decline of the heart rate was never observed under dibenamine.

using different autonomic-blocking agents or to fit these into the maze of known patterns of autonomic controls. It is possible only to speculate concerning the probable mode of action of dibenamine itself. It seems, however, that a number of clear cut changes occur which lend themselves to interpretation:

1. Little change is noted in the resting normal individual, apparently because bodily functions at rest proceed automatically and without excessive nervous control. Wherever and whenever a delicate autonomic balance appears to govern a normal

or abnormal resting state, blocking of the adrenergic component must result in tipping the scale in favor of the parasympathetic system. This may explain the occasional occurrence of congestion of the nasal mucosa and regularly constricted pupils following

TABLE III
EFFECT OF DIBENAMINE HYDROCHLORIDE IN MAN
(5 MG/KG.)

The following excitatory effects of the adrenergic systems are:

1. Blocked:
 - (1) Dark adaptation (pupillary dilatation in dim light)
 - (2) Reflex rise in vascular pressures (arterial and venous)
 - (3) Secondary reflex bradycardia with escape phenomena
 - (4) Secondary reflex changes in ventricular complexes
2. Partially blocked or the blocking is questionable:
 - (1) Resting vascular tone (arterial and venous)
 - (2) Sweat secretion*
 - (3) Myocardial stimulation (ectopic foci)
3. Not blocked:
 - (1) Rise in cardiac output
 - (2) Constriction of certain capillary regions
 - (3) Epinephrine sinus tachycardia
 - (4) Epinephrine changes of ventricular complexes
 - (5) Increase in electrical systole
4. Increased:
 - (1) Response of blood glucose to parenteral epinephrine

* Sweat secretion is regulated by the parasympathetic system although mediated through sympathetic fibers.

administration of dibenamine in all individuals. In certain examples of peripheral vascular disease this concept may be used in referring to an excessive "sympathetic tone" which has been released when a temporary increase in peripheral blood flow is demonstrable after the injection of dibenamine. Such changes were never observed in normal individuals. On the same basis one expects a reduction of hypertensive blood pressure levels toward a more normal range. This was demonstrated in rats made hypertensive¹ and occasionally occurred in man but was never striking. Failure to lower abnormal blood pressure levels in man may be attributed to the relatively small doses which can be administered with safety. Whether the toxic effects (nausea, convulsions and perseverations) are caused by an

impaired autonomic balance in the central nervous system itself remains a matter of speculation at present.

2. Reflex stimulation of the adrenergic system, particularly of the vascular tree but also of other systems (pupils) appears to be blocked effectively. Whenever this was not observed the changes looked for may not have been based on epinephrine mediated reflex vasoconstriction alone (cold pressor test) or organic disease may have obviated a normal response. Failure of orthostatic hypotension to occur upon the administration of dibenamine was noted when voluntary muscular contraction overcame the pooling of blood in the veins, or when occlusive vascular disease was present to such an extent that the normal elasticity of the vascular walls had been lost. It was significant that in some of the cases in which no response to dibenamine could be elicited reflex vascular relaxation of the extremities secondary to heating other parts of the body was likewise absent, and "over-swing" of the temperature following cooling of a finger failed to occur. A very excessive "sympathetic tone" not readily overcome by the usual doses of dibenamine or other measures may also have been a factor in these cases.

3. The response of the resting subject to the injection of sympathomimetic compounds was always significantly altered under the influence of dibenamine, although certain isolated reactions proceeded unchanged. Compounds whose main action consists in peripheral, arterial and venous vascular constriction appear to be deprived of their effect and can be injected in large amounts without causing any change in arterial and venous pressures. The effects of these compounds upon the heart secondary to reflex vagal stimulation occasioned by the rise in blood pressure are, of course; likewise absent. (Excessive slowing of the sinus node with escape of lower centers,

"vagal" T wave changes and alterations in A.V. conduction).

The effects of injected epinephrine may be summarized by stating that the results following rapid intravenous administration are so altered as to resemble the effects usually seen after subcutaneous injection: diastolic pressure falls and systolic pressure rises, resulting in a considerable increase in pulse pressure.¹¹ This is the consequence of peripheral vascular dilatation and may be explained by assuming that only the excitatory effects ("sympathin E") but not the inhibitory effects ("sympathin I") are influenced by dibenamine (Fig. 9.) This is further borne out by the obvious protection afforded by dibenamine for epinephrine-induced cardiac irregularities in man and animals. Peculiarly, other excitatory effects remain apparently uninfluenced (tachycardia, cardiac output, circulation time and capillary constriction of certain skin areas). The direct effects of epinephrine upon the heart muscle undergo no alterations after dibenamine has been given (T wave changes and lengthening of the electrical systole). Experiments testing many of the other known effects of epinephrine are now in progress.

The site of action of dibenamine must remain a matter of speculation as long as the mechanism of action of the sympathetic system is not clearly understood; however, a few negative statements can be made. Obviously, dibenamine does not act peripherally as a simple vasodilator like the nitrites (pupillary effects and blocking of ectopic foci). It cannot be considered an autonomic ganglion blocking agent similar to tetraethyl ammonium¹⁷ because it does not alter the resting autonomic tone in general and has no actions other than those specifically directed toward certain effects of the adrenergic system. An effect of dibenamine on the central nervous system appears equally unlikely because of the peculiar

specificity of its action and the absence of central effects other than those regarded as toxic. A not infrequent action of blocking agents in general consists in replacing the effector substance at its site of action. This has been assumed for anti-histaminic agents (benadryl and pyribenzamine), for antidotes of the dithiol group in metallic poisoning (BAL), and for the antagonism which exists between paraminobenzoic acid and methionine to the sulfonamides. On the basis of Cannon and Rosenbluth's theory of sympathetic mediation,¹⁷ it may be postulated that a compound is formed in the effector cell where the mediator substance released by sympathetic nerve endings (M) is combined with one of two kinds of hypothetical substances, one inhibitory (I) and one excitatory (E). The final active compound is either sympathin E (ME) or I (MI). By analogy with other blocking compounds, replacement of the hypothetical substance E by dibenamine might be postulated to result in an ineffective MD compound instead of the effective ME combination. Formation of MI resulting in inhibitory effects, including vasodilatation, would not be affected. (Fig. 9.) This would explain the interesting and highly specific action of dibenamine upon certain excitatory effects of the adrenergic system. The lack of blocking of other effects hitherto thought to be excitatory has found no explanation at present.

The very intriguing therapeutic implications which compounds of this kind may have in spite of the disappointing results observed so far need not be considered at this time.

SUMMARY

1. Dibenamine (dibenzyl- β -chloroethylamine), a compound shown to possess certain sympatholytic properties in animals, was administered to fifty-four patients. Only the intravenous route was found to be

safe and to yield consistent results. Given orally dibenamine was poorly tolerated and its action was unpredictable.

2. The effective single intravenous dose appeared to be 4 to 6 mg./Kg. bodyweight (0.25 to 0.50 Gm. per patient). The height of the pharmacological action of dibenamine usually occurred during the first twenty-four hours. In some patients the response to standard sympathetic stimuli appeared to be changed for several days following a single injection.

3. Following the administration of dibenamine, it was seen that some of the excitatory effects of sympathin released by stimulation of the adrenergic system were altered and appeared completely blocked when tested in the resting patient, following standard exercises or upon the intravenous injection of sympathomimetic compounds. Some of the expected responses to parenterally administered epinephrine remained unchanged or appeared potentiated by dibenamine.

The authors are indebted to Dr. L. S. Goodman for advice and criticism.

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Diagnostic Value of the Secretin Test*

Including a Report of Nineteen Operated or Autopsied Cases with Anatomical Studies of the Pancreas

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NEW YORK, NEW YORK

ALTHOUGH Bayliss and Starling discovered secretin in 1902, it was not until 1933 that this substance was isolated in crystalline form by Hammarsten and his collaborators.¹ Later a less pure preparation, one suitable for intravenous use in man, became available commercially.† It is heat stable, free from allergens and cholecystokinin and has caused few untoward reactions. With the use of a specially constructed double barrel gastroduodenal tube and constant suction, Agren and Lagerlöf^{2,3,4} succeeded in quantitatively obtaining the duodenal contents uncontaminated for the most part by gastric juice. With this technic it became possible to study the effect of a measured dose of secretin on the external secretion of the pancreas. All observers who have reported their findings agree that the test showed great promise of being a valuable diagnostic procedure. However, the number of proven normal and pathological cases studied is still relatively small, and doubt exists as to the normal range of values and clinically significant variations. Diamond and Siegel,^{5,6} who reported the largest series studied in this country, obtained results almost identical with those of the original Swedish investigators. Pratt, Brugsch and Rostler⁷ obtained considerably lower values in sev-

eral psychoneurotic patients, and stated "to assume as has been done that such values indicate pancreatic hypofunction of clinical significance lacks justification until supported by additional evidence not yet obtainable."

The present study was completed in 1942. The test was performed forty-three times on thirty-four individuals all of whom, with one exception, had abdominal complaints. The delay in publishing these results, except for a short report of two of the cases,⁸ resulted in the opportunity of reviewing the subsequent course of the patients four years later. During this interval the pancreas of eight patients had been inspected and palpated at operation, and it was examined histologically in eleven others. In twelve additional patients prolonged clinical observation left little doubt as to the diagnosis, and the results in this group are included for comparative purposes. In three patients the diagnosis is still obscure and the results are not included in this report.

TECHNIC AND CHEMICAL METHODS

Since we wished to compare our results with those of Agren and Lagerlöf^{2,4} and Diamond and his associates^{5,6} the technic and chemical methods which they describe were used, with minor modifications.

After an overnight fast a specially con-

* From the New York Hospital and the Cornell University Medical College, New York, N. Y. This investigation was aided by a grant from the Council on Pharmacy and Chemistry of the American Medical Association. Mary Cooper, B. S. and Elsa Nussbaumer gave technical assistance.

† Pancreatost, Astra Chemical Company, Sweden.

structed two-barrel tube* was passed to the proper position under fluoroscopic control. Instead of the water suction pump used by others, a small electric pump was found to be more satisfactory in that it is silent and maintains a more constant negative pres-

Bicarbonate concentration in milliequivalents

Hydrogen ion concentration

Concentration in units per cc. of diastase, trypsin and lipase

The total amount of bicarbonate was cal-

VOLUME

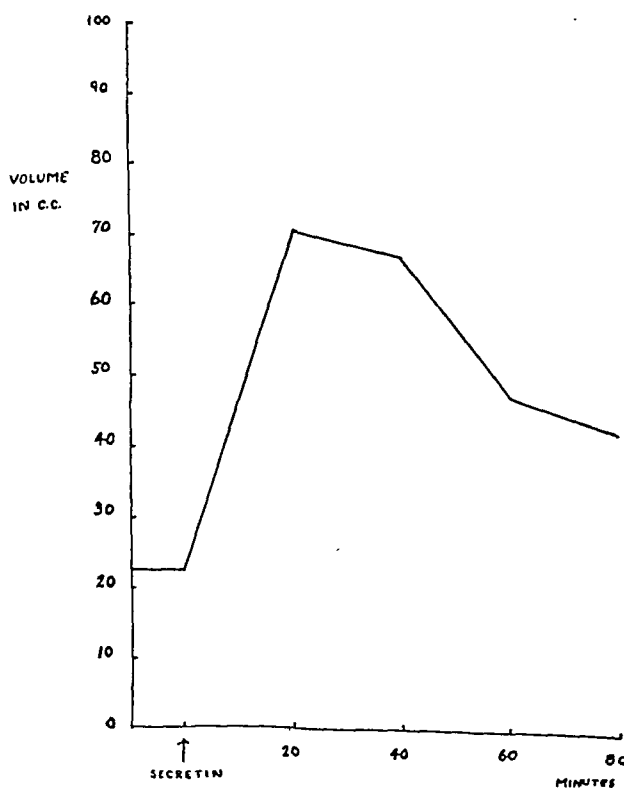


FIG. 1. Average volume per fraction.

sure. A negative pressure of 20 to 30 mm. of mercury was found to be sufficient. With higher pressures bleeding was occasionally encountered. The duodenal contents were collected during a twenty-minute period prior to the injection of 1 clinical unit of secretin per Kg. of body weight, and in twenty-minute fractions for sixty minutes following the secretin. Each fraction was placed in a refrigerator as soon as it was collected.

The fractions were measured for volume and the following determinations were made of each fraction:

* Davol Rubber Company.

culated in terms of N/10 NaHCO_3 and the total of each enzyme in units (2) for the sixty-minute period following the secretin injection. Since some investigators have reported their findings in values per Kg. of body weight the weights of the subjects are included in the tables.

Unfortunately, bicarbonate determinations were not made in the first nine cases of this series. When more than one test was made on the same individual the highest values obtained were given except in Case 2 in which all the values were recorded.

The method of Crandell and Cherry¹⁶ was used for the lipase determination but its

use is not recommended as the olive oil emulsion was found to be unstable. It was noted that the values for lipase varied with the age of the olive oil emulsion. Although some of the readings were corrected by doing comparative tests with a fresh emulsion, the

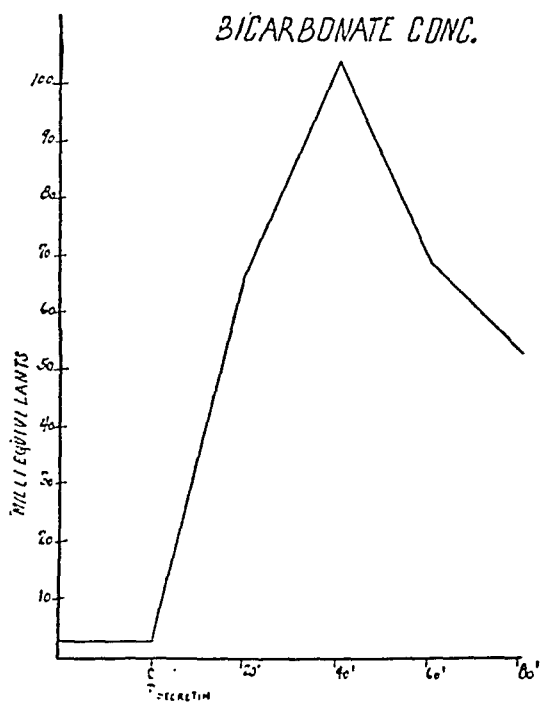


FIG. 2. Average bicarbonate concentration per fraction.

lipase values reported here are probably inaccurate to some extent, although they are comparable to values reported by others using the same method.^{5,6} After this study was completed Lagerlöf¹⁵ advised against the use of this method. He also pointed out the advisability of adding glycerin to the collecting bottles and of keeping them chilled to prevent inactivation of the trypsin during the recovery and storage of the duodenal juice. With this change in technic he obtained higher trypsin values in his more recently reported series.¹⁵

Normal Material. Group I A: The normal series consists of five cases; in two (Cases 6 and 10) the pancreas presented a normal appearance at operation, and in three (Cases 13, 32 and 36) the pancreas was examined histologically at autopsy and

was found to be normal. The established diagnoses in this series were as follows:

Case 6. Gallstones

Case 10. Stones in gallbladder and common duct; obstructive jaundice

Case 13. Cirrhosis of the liver; jaundice

Case 32. Cirrhosis of the liver; jaundice

Case 36. Chronic hepatitis and splenomegaly; jaundice

Group I B: Twelve additional subjects, including one medical student without complaints, were sufficiently observed so that it was reasonably certain that no pancreatic disease was present at the time of the test. This group also included a patient (Case 20) with a sprue-like syndrome in whom autopsy twenty months after the test was performed showed lymphosarcoma of the small intestines with invasion of the head of the pancreas. He developed terminal jaundice. It is believed that at the time of the test the pancreas was probably normal. The clinical diagnoses are listed below:

Case 8. Anxiety neurosis

Case 14. Non-tropical sprue

Case 21. Gallstones

Case 25. Psychoneurosis

Case 27. Chronic hepatitis

Case 28. Gallstones

Case 31. Psychoneurosis

Case 33. Duodenal ulcer

Case 35. No disease

Case 20. Lymphosarcoma of small intestines with a sprue-like syndrome

Case 12. Acute hepatitis

Case 30. Common duct stone with jaundice

Case 14. Pylorospasm

Pathological Material. Group II: This group consists of thirteen cases with demonstrated disease of the pancreas at operation or at autopsy, as follows:

Acute pancreatic necrosis (Cases 2 and 9)

Chronic pancreatitis (Cases 11, 16, 22, 3 and 4)

Carcinoma of the tail of the pancreas (Cases 1 and 24)

Carcinoma of the head of the pancreas
(Cases 3, 26 and 29)

Metastatic carcinoma of the liver, probably
from the pancreas (Case 34)

Results. The results are presented in
Tables I to IV and in Figures 1 to 3. In

TABLE IA
PANCREAS NORMAL AT OPERATION OR AUTOPSY

Case No.	Weight Kg.	Volume cc.	pH	Bicarbonate		Dias- tase Units	Tryp- sin Units	Lipase Units
				High- est Conc.	Total Out- put			
6	58.4	212	8.2	738	62	12,835
10	59.5	345	7.6	88	235	247	47	18,400
13	49.3	177	8.2	94	144	223	46	6,534
32	43.3	94	8.1	76	62	325	28	5,987
36	55.5	199	8.1	118	197	360	32	7,735

Tables I and II the value of each component
is presented as the total for a sixty-minute
period following the injection of secretin,

TABLE IB
PANCREAS BELIEVED TO BE NORMAL

Case No.	Weight Kg.	Volume cc.	pH	Bicarbonate		Dias- tase Units	Tryp- sin Units	Lipase Units
				High- est Conc.	Total Out- put			
8	37.1	218	8.0	515	74	14,145
14	52	216	8.1	86	163	409	39	7,542
21	66.6	172	8.0	116	151	476	56	10,965
25	47	238	7.8	84	137	325	71	16,403
27	53.1	123	8.1	112	113	344	29	5,779
28	87.9	245	8.0	134	242	450	40	16,935
31	75	94	8.1	106	80	222	22	5,853
33	44.5	188	8.1	120	182	798	40	13,827
35	79.8	191	8.3	130	166	401	46	9,497
20	44.0	134	8.2	94	110	436	37	8,431
12	65.9	128	8.4	124	134	238	33	7,641
30	49.5	205	8.0	104	131	307	68	13,926
19	63.7	170	7.6	76	95	376	44	10,689

except that the maximal concentration of
bicarbonate and the highest pH obtained
in this period are included. In Tables III
and IV the maximum concentration of the
enzymes obtained during this period are
listed.

The range of values in the small series
without pancreatic disease was as follows:

Volume..... 94 to 345 cc.

Bicarbonate

Maximum concentration. 76 to 134 milliequivalents

Total in sixty minutes.... 62 to 242 N/10 NaHCO₃.

Dias-
tase

Maximum concentration. 1.26 to 8.8 units per cc.

Total in sixty minutes.... 222 to 798 units

Trypsin

Maximum concentration. 0.20 to 0.55 units per cc.

Total in sixty minutes.... 22 to 74 units

Lipase

Maximum concentration. 40.5 to 77 units per cc.

Total in sixty minutes.... 5779 to 18,400 units

COMMENT

Volume. Immediately following the in-
jection of secretin the rate of flow of the

TABLE II
PANCREAS DISEASED AT OPERATION OR AUTOPSY

Case No.	Weight Kg.	Volume cc.	pH	Bicarbonate		Dias- tase Units	Tryp- sin Units	Lipase Units
				High- est Conc.	Total Out- put			
A. Acute Pancreatitis								
2 a	74.6	75.1	8.3	153L	25	7,601
b	80	80L	8.5	76L	10L	2,486L
c	80.8	81L	8.5	119L	13L	2,763L
9	70	237	7.8	109L	49	9,492

B. Chronic Pancreatitis

11	39.5	152	8.2	104	149	195L	(9.1)	9,529
16	72	161	7.6	38L	53L	165L	40	8,680
22	64	187	7.7	114	153	150L	34	12,747
3	45.5	149	8.2	109L	33	12,778
4	57	175	8.1	268	14L	8,011

C. Carcinoma of Tail of Pancreas

1	60	137	8.1	203L	23	10,046
24	71	186	7.7	78	117	401	38	12,628

D. Carcinoma of the Head of the Pancreas

7	100	60L	8.0	21L	13L	1,917L
29	57.6	77L	8.1	64L	34L	39L	14L	1,878L
26	84	501L	7.8	96	382L	673L	115L	31,886L

E. Metastatic Carcinoma of Liver, probably from the Pancreas

34	77.8	130	8.4	102	101	62L	19L	5,697L
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Note: Values followed by L are not within the normal range.

duodenal contents rapidly increased, usu-
ally reaching its maximum in the first
twenty minutes, occasionally in the second
twenty minutes. The maximum twenty-

minute volume varied from 2.2 to nine times the presecretin volume. The average sixty-minute volume in the nonpancreatic cases was 186 cc., the minimum 94 cc. and the maximum 345 cc. In sixteen of the eighteen nonpancreatic cases the volume exceeded the minimal normal value of 135 cc. which Diamond and his co-workers^{5,6} obtained. Lagerlöf¹² obtained an average volume of approximately 150 cc., a range of 104 to 266 cc. Pratt, Brugsch and Rostler,⁷ when they used constant suction, obtained an average volume of 174 cc. and a lowest normal volume of 82 cc. In this study abnormally low volumes were obtained in two patients with carcinoma of the head of the pancreas (60 cc. and 77 cc.) and one case following pancreatic necrosis showed a consistently low volume in three tests (75 cc., 80 cc. and 81 cc.). Another patient with carcinoma of the pancreas with functional overactivity had the greatest volume in this series, 501 cc.

TABLE III CASES WITHOUT PANCREATIC DISEASE MAXIMUM CONCENTRATION OF ENZYMES			
Case No.	Diastase	Trypsin	Lipase
6	6.9	.345	68
10	1.26	.255	64
13	1.6	.28	40.5
32	5.6	.465	62.3
36	8.0	.485	41.5
8	2.9	.435	65
14	2.4	.20	41.5
21	3.6	.40	63
25	2.4	.365	70.5
27	8.8	.55	49
28	2.8	.30	73
31	4.8	.425	66.1
33	8.0	.32	77
35	3.2	.51	53
20	4.4	.34	54
12	3.2	.29	62.8
30	1.7	.36	72.5
19	2.96	.51	76

Bicarbonate. Figures 2 and 3 show the average concentrations of bicarbonate and the total amount in each fraction in the cases without pancreatic disease. The maxi-

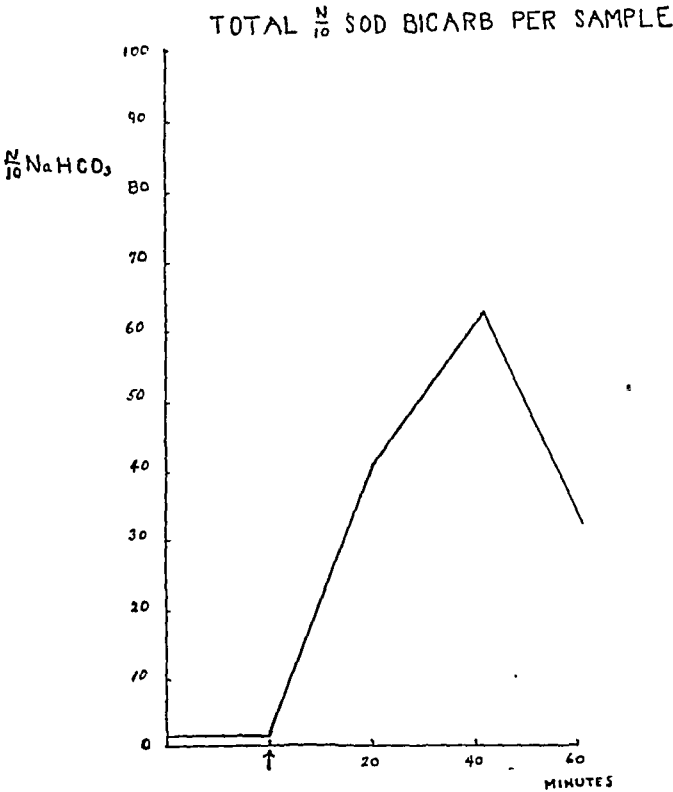


FIG. 3. Average bicarbonate content per fraction.

imum level of both is reached in the second twenty-minute period, somewhat later than the maximum volume. The pH became most alkaline at the same time, reaching 8.0 or higher in sixteen of the eighteen cases. The maximum bicarbonate concentrations in eighteen nonpancreatic cases ranged from 76 to 134 milliequivalents. Agren and Lagerlöf⁴ obtained 94 to 137 milliequivalents, Diamond and Siegel⁵ 90 to 130, Pollard, Miller and Brewer¹⁰ 75 to 141, Pratt, Brugsch and Rostler⁷ 50 to 115. The latter investigators, however, did not always use constant suction, which probably explains some of their low values. Five of our nonpancreatic cases had values of less than ninety. In the cases with pancreatic disease the lowest concentration was 38 milliequivalents in Case 16, and 64 milliequivalents in Case 29. The total bicarbonate secreted in sixty minutes ranged from 62 to 242, expressed as N/10 NaHCO₃, in our non-pancreatic cases. Only one case had less than 80. Lagerlöf¹² in forty-two normal cases obtained values of 82 to 301. Our lowest value of 34 occurred in Case 29, one with carcinoma of the pancreas. The highest value was also obtained in a case of carcinoma with hypersecretion, 382 (Case 26). Case 16, in which the biopsy showed chronic pancreatitis while the clinical course was that of carcinoma, had a total bicarbonate secretion of 53.

Enzymes. The concentrations of the enzymes were usually highest in the duodenal contents before the secretin injection and tended to fall as the volume of the secretion increased and to rise again in the last fraction. Occasionally, however, the concentration rose for a short time immediately following the secretin. This occurred most frequently in the case of lipase. The three enzymes often varied in concentration independently of each other. Diastase showed the greatest variability, the range in the non-pancreatic cases being from 1.26 to 8.8

units per cc. The lowest values were obtained in Case 9 (acute pancreatitis), 0.5 and in two cases of carcinoma, Case 7, 0.53 and Case 29, 0.68. In two patients with carcinoma, one with acute pancreatitis and five with chronic pancreatitis, normal

TABLE IV
CASES WITH PANCREATIC DISEASE
MAXIMUM CONCENTRATION OF ENZYMES

Case No.	Diastase	Trypsin	Lipase
Acute Pancreatitis			
2 a	3.04	.345	76
b	1.9	.345	51
c	2.2	.31	52.5
9	0.5 ₁	.23	45
Chronic Pancreatitis			
11	3.8	71.8
16	2.1	.34	56
22	1.2	.20	70
3	1.4	.39	92
4	2.2	.21	51
Carcinoma of Tail of Pancreas			
1	1.94	.38	83
24	5.2	.51	67
Carcinoma of Head of Pancreas			
7	0.53 ₁	.21	33 ₁
29	0.68 ₁	.80	28 ₁
26	1.92	.26	65.5
Metastatic Carcinoma of Liver, Probably from Pancreas			
34	1.4	.26	54.5

Note: Values followed by ₁ are below the lowest figures obtained in the normal series.

values were obtained. The concentration of trypsin varied normally from 0.2 to 0.55 units per cc. and all of the pathological cases showed values within this range. Lipase concentrations varied in the non-pancreatic cases from 40.5 to 76 units per cc. Only two patients, both with car-

cinoma of the pancreas, showed lower values: 33 and 28 units per cc. (Cases 7 and 29). In Table iv the concentrations of the enzymes are listed for cases with pancreatic disease. It is of interest that none of our pathological cases showed a complete absence of enzymes in all fractions, since Comfort, Parker and Osterberg⁹ concluded that the total absence of pancreatic enzymes alone may be taken as evidence of abnormal pancreatic function if the pancreatic enzymes are absent from more than one specimen.

The total units of enzymes obtained in sixty minutes proved to be a more frequently useful criterion of pancreatic pathology than their concentrations. In the eighteen patients without pancreatic disease, the lowest values obtained in sixty minutes were: diastase 222 units, trypsin 22 units and lipase 5,779 units. The diastase value is somewhat lower than the minimum of 300 which the Swedish investigators found in normal subjects, but considerably higher than Pratt, Brugsch and Rostler obtained. Our values for trypsin and lipase agree fairly well with those of Agren and Lagerlöf. The most frequent change noted in the cases with pancreatic disease was a decrease in diastase; this occurred in ten of the thirteen cases with pancreatic disease and was the only abnormal finding in six cases. In only one patient was the diastase value normal in the presence of any other abnormal value, such as a low trypsin value (Case 4). This seems to support Lagerlöf's statement¹² that diastase possesses the highest functional significance. Trypsin and lipase values were less easily disturbed; a decrease in both was found in one case of acute pancreatitis and in three cases of carcinoma of the pancreas.

Bile. Prior to the injection of secretin, bile was present in the duodenal contents. After the secretin was injected all visible evidences of bile disappeared for a variable period of time if a normally functioning

gallbladder was present; otherwise, the bile color persisted throughout the test period. The mechanism by which the flow of bile is diverted to the gallbladder requires further investigation, but this response¹³ proved to be a reliable test of gallbladder function in twenty-nine of thirty-one cases, a degree of accuracy comparable with Lyon's method and with the Graham test. It proved to be of particular value in a patient with acute hepatitis in whom no shadow was obtained by x-ray because of impaired liver function. During convalescence a normal gallbladder was visualized by x-ray.

FINDINGS IN PANCREATIC DISEASE, WITH CASE REPORTS

Acute Pancreatitis. Two patients were tested following an operation for acute necrosis of the pancreas. Three tests were performed on one patient.

CASE 2. A forty-three year old white male chauffeur was admitted to the New York Hospital on January 6, 1941 complaining for four days of an abdominal pain. Aside from the usual childhood diseases and a fracture of the right leg eight years before, his past history was negative except for upper abdominal discomfort after meals, which he had had for several years and which was relieved by soda and peppermint. Four days before his admission he had a similar attack. Two days before he took a large dose of castor oil. Following this he had generalized abdominal pain, nausea and vomiting.

Physical examination showed an acutely ill, well nourished patient in acute abdominal distress, with a rapid pulse and tenderness of the abdomen which was most marked in the mid-epigastrium where there was extreme tenderness and spasm. A flat plate of the abdomen was negative. Following a short period of observation during which he received intravenous fluids and a blood transfusion, he was explored.

Exploration showed the presence of a large amount of rusty, cloudy fluid in the peritoneal cavity and a moderately swollen pancreas which

was studded with small, gray necrotic areas containing thick, grayish-yellow fluid. Cultures of this fluid showed no growth. Two drains were placed in the foramen of Winslow and two in the pancreas.

Postoperatively the patient had a rather stormy course; his temperature remaining elevated until the sixth postoperative day. It rose again on the eleventh day and a wound infection was found. When adequate drainage was established his general condition improved remarkably.

The secretin tests were performed approximately five, eleven and seventeen weeks following operation.

Results of Secretin Tests	Feb. 11, 1941	Mar. 25, 1941	May 6, 1941
Volume in sixty minutes . .	75	80	81
Highest pH	8.3	8.5	8.5
Diastase in sixty minutes . .	153	76	119
Trypsin in sixty minutes . .	25	10	13
Lipase in sixty minutes . . .	7601	2496	2763

These results indicate a progressive deterioration of pancreatic function. Subjectively, the patient had no complaints except that he was not regaining his strength as quickly as he had expected.

CASE 9. A sixty-two year old woman was admitted to the New York Hospital on March 19, 1941, complaining of abdominal pain of six days' duration and diarrhea for two days. Her past history was essentially negative except for belching and pain in the right upper quadrant and epigastrium, which radiated to the back and had been present for the past ten years. This came on after almost every meal which contained fatty food and was relieved by hot water and bicarbonate of soda. Six days before admission, after a light breakfast, she had severe right upper quadrant pain and vomiting. The vomiting stopped, but the pain persisted.

Physical examination showed an acutely ill patient with fever, rapid pulse, a distended bladder and tenderness in the right upper quadrant. The white blood count was 60,000 with 57 per cent mature and 27 per cent immature polymorphonuclear leukocytes. One specimen of

urine contained sugar while several others were negative.

The day following admission an exploratory laparotomy revealed the presence of a brownish cloudy fluid in the peritoneal cavity which subsequently proved to be sterile. A markedly distended pancreas was found to which a large mass of omentum was adherent. Small patches of golden-yellow fat necrosis were seen in the omentum. On opening the pancreatic capsule the pancreas appeared to be completely necrotic throughout its length. Four drains were inserted and the abdomen closed. After a stormy convalescence, during which there was a prolonged discharge of necrotic slough and pus from the wound, she was discharged from the hospital on June 2, 1941.

On follow-up visits in April, 1942, and May, 1943, she had no complaints, but a large ventral hernia was present.

A secretin test seven weeks after operation gave the following results:

Volume in sixty minutes	237 cc.
Highest pH	7.8
Diastase in sixty minutes	109 units
Trypsin in sixty minutes	49 units
Lipase in sixty minutes	9492 units

These findings are within normal limits except for the diastase, which is less than half of the normal value.

Chronic Pancreatitis. Five patients with chronic pancreatitis were tested. In two (Cases 3 and 4), the pancreas was described as enlarged and indurated at operation on the biliary tract. In the other three cases histological studies of the pancreas were made and are reported in detail below. Case 11 is of particular interest, as the pancreatic juice was obtained from a pancreatic fistula unmixd with the duodenal secretion or bile. All five cases showed low values of one or more factors; four had low diastase values, one a low trypsin secretion and one a decreased amount of bicarbonate. All volumes were within normal limits.

CASE 11.* This fifty-six year old man was admitted to St. Luke's Hospital on March 31,

* I am indebted to Dr. William F. MacFee for the opportunity of studying this case.

1941, for the second time. During a previous admission in 1939 he had had epigastric pain and passed tarry stools, although an ulcer was not demonstrated by x-ray examination at that time. He complained of epigastric fullness and vomiting for a duration of four months. He also stated that he had lost 17 pounds during the past year and had become weak and irritable.

Physical examination was essentially negative. X-ray examination showed a markedly dilated stomach with deep hyperactive peristalsis and a large twenty-four-hour retention. The duodenal cap could not be filled by manipulation. Pyloric obstruction due to an ulcer was suspected.

Laboratory findings were within normal limits except for a low serum protein level (4.85 Gm. per cent) and moderate anemia. After a period of preparation a subtotal gastrectomy was performed and a posterior gastrojejunal anastomosis. A duodenal ulcer was found on the posterior wall eroding into the pancreas for about 2 cm. in diameter and 1 cm. in depth. The ulcer was left *in situ* and a drainage tube was inserted in this region. A large mesenteric node was removed and showed an area of tubercle formation with groups of epithelioid cells and giant cells of the Langerhans type.

Following the operation, a large amount of clear fluid drained out through the drainage tube. He began to pass large, foul stools and became markedly distended. Examination of this fluid showed it to be rich in pancreatic enzymes. The fluid was then returned to his gastrointestinal tract through a Levin tube. Within two days the distention and diarrhea subsided and his general condition was greatly improved. It was noted that the amount of drainage increased immediately after meals and during the night. On May 29, 1941, a symmetrical glove-type of dermatitis was noted on both hands. On May 26, 1941, the drainage fluid was collected for a twenty-minute period. The usual dose of secretin was then injected and further collections were made in fractions for sixty minutes. On May 31, 1941, he suddenly went into coma, had convulsions and died.

At autopsy, the left upper lobe of the lung showed extensive fibrosis with moderate lymphocytic infiltration. There was also a large calcified

area and another area of fresh caseation. The renal tubules showed marked cloudy swelling. In the pancreas there was a well marked increase in the interlobular fibrous tissue. Sections through the sinus tract in the head of the pancreas showed it to be lined by dense fibrous connective tissue. On the surface there was a thin layer of necrotic tissue. The microscopic diagnoses were: Localized chronic pancreatitis, fibrocaceous pulmonary tuberculosis and chronic passive congestion of the lungs and liver.

The results of the secretin test are given in detail below:

Sample	Time, min.	Volume, cc.	Sp. Gr.	pH	Bicarbonate Conc., milliequivalents
Control	20	25.0	1.016	7.48	34
1	20	55.5	1.013	7.80	82
2	20	48.0	1.012	8.20	104
3	20	48.0	1.012	8.20	104

The control fraction was opalescent, the first fraction slightly opalescent and the last two clear. The concentrations and amounts of enzymes were as follows:

Sample	Diastase		Trypsin		Lipase	
	Conc.	Amt.	Conc.	Amt.	Conc.	Amt.
Control	3.8	95.0	.02	0.5	70.0	1750
1	1.4	77.7	.08	4.4	71.8	3984.9
2	1.4	67.2	.04	1.9	56.3	2702.4
3	1.04	49.9	.06	2.8	59.2	2841.6
Total in 60 minutes		194.8		9.1		9528.9

The total bicarbonate in sixty minutes was 149.1 N/10 NaHCO_3 .

These findings are within normal limits except for the diastase, which is slightly lower than our normal low value of 222 units. No significance can be attached to the trypsin value since it was not activated.

CASE 16. This seventy year old widow was admitted to the Memorial Hospital on March 26, 1941, complaining of weakness and loss of

weight of two months' duration and of painless jaundice, pruritus, dark urine and gray colored stools for three weeks' duration.

Physical examination showed the presence of jaundice, an enlarged liver and a separate globular mass extending to 2 inches above the umbilicus. X-ray studies showed a normal gastrointestinal tract. Urinalysis showed sugar present and the blood sugar level was elevated. On April 14, 1941, she was explored with the preoperative diagnosis of a carcinoma of the head of the pancreas. The operative findings were: an enormously distended gallbladder which contained twenty-six small, hard, black stones; the liver was grossly bile-stained but otherwise normal; a hard nodular mass was felt in the head of the pancreas and a wedge biopsy taken. A cholecystogastrostomy was performed. The patient was treated for diabetes and discharged May 24, 1941.

The biopsy was reported as showing interstitial pancreatitis with fat necrosis. There was no microscopic evidence of carcinoma in the sections examined.

Although the jaundice was relieved she continued to complain of weakness, frequent nausea and later of abdominal pain. Her weight loss continued and she died at home on August 19, 1941. An autopsy was not performed.

Although the microscopic diagnosis was chronic pancreatitis, the clinical course was very suggestive of carcinoma of the pancreas.

A secretin test was performed on July 9, 1941, after the cholecystogastrostomy, with the following result:

Volume in sixty minutes.....	161 cc.
Highest pH.....	7.6
Bicarbonate	
Highest concentration.....	38 milliequivalents
Total in sixty minutes.....	53 N/10 NaHCO ₃
Diastase in sixty minutes.....	156 units
Trypsin in sixty minutes.....	40 units
Lipase in sixty minutes.....	8680 units

The bicarbonate and diastase values are low; the others are within normal limits.

CASE 22. This case was reported previously,⁸ except for the detailed autopsy findings in regard to the pancreas. The verified diagnosis was carcinoma of the common bile duct. The secretin test, we then stated, indicated "a

normal response, except for a somewhat low diastase value resembling the results seen in pancreatitis." On gross examination several cysts were scattered throughout the organ. Subsequently, a microscopic study of the pancreas was reported as follows: "There is considerable fibrosis, both inter- and intralobular, but the acini and islands are in general well preserved. In a few ducts there appears to be metaplasia to a transitional epithelial lining. In others there is a papilloma-like growth of the duct epithelium. Included in the section is one of the cystic structures described grossly. This has a connective tissue wall and is lined on the inside by a single layer of cuboidal to slightly columnar epithelium resembling that of the pancreatic ducts. Adjacent to this are several cross sections of somewhat dilated and apparently partially occluded pancreatic ducts. In several places in the section there is moderate round cell infiltration." Anatomical diagnosis included "hyperplasia of branches of pancreatic duct with cyst formation, fibrosis of pancreas; metaplasia of duct epithelium, slight."

The results of the secretin test are included in Table II. The diastase was low, other factors were normal.

CARCINOMA OF THE TAIL OF THE PANCREAS

In two patients with carcinoma of the tail of the pancreas, both proved by microscopic sections, both being inoperable, the following results were obtained:

	Case 1	Case 24
Volume.....	137 cc.	186 cc.
Highest pH.....	8.1	7.7
Bicarbonate		
Highest Conc.....		78 milliequivalents
Total in 60 min.....		117 N/10 NaHCO ₃
Diastase in 60 min.....	203 units	401 units
Trypsin in 60 min.....	23 units	38 units
Lipase in 60 min.....	10,046 units	12,628 units

These values are within normal limits except for a slight decrease in diastase in Case 1.

CARCINOMA OF THE HEAD OF THE PANCREAS

CASE 7. This sixty-two year old woman was admitted to New York Hospital on February 28, 1941, complaining of jaundice and itching of five weeks' duration. She had lost 55 pounds in the past two months and 100 pounds in the past year. Since the onset of jaundice she had vomited after every meal, but at no time complained of pain. Her past health had been excellent except for a cholecystectomy for gallstones twenty years before, at which time she was not jaundiced. She stated that twenty years before, following removal of her left ovary, her menstrual periods ceased and she began to gain weight, so that one year prior to admission her weight was 343 pounds. At the time of admission her weight was 244 pounds.

Physical examination showed jaundice, obesity, evidence of weight loss and mild hypertension.

Laboratory tests showed an icteric index of 100 on admission, 135 one week later. Stools were consistently negative for blood and bile. A gastrointestinal series was negative. The prothrombin time was normal.

She vomited frequently and felt nauseous most of the time.

On the eleventh day after admission an exploratory laparotomy was carried out. The common duct was found to be dilated. In the region of the head of the pancreas there was a hard nodular lesion about 6 cm. in diameter and running along the body of the pancreas there was a similar hard mass which seemed to be spreading from the mass in the head of the pancreas. This was thought to be carcinoma. The common duct was explored and nothing found but the mass noted in the head of the pancreas. A scoop was introduced and no stones were found. A T-tube was inserted in the common duct and the defect repaired.

Unfortunately, no biopsy was done. She was discharged to another hospital for terminal care on April 16, 1941 and died on August 9, 1941.

During the secretin test no bile was obtained through the tube, but blood was present in the duodenum. No increase in volume occurred after the secretin was injected. The following values were obtained:

Volume.....	60 cc.
Highest pH.....	8.0
Diastase in 60 min.....	21 units
Trypsin in 60 min.....	13 units
Lipase in 60 min.....	1917 units

These values are all considerably below normal.

CASE 26. This case was previously reported⁸ as an example of an extremely active response of a carcinomatous pancreas in which, although the main pancreatic duct was occluded by the tumor, a large accessory duct was patent. At operation the tail of the pancreas, which appeared normal and constituted about one-sixth of the organ, was implanted into the open end of the jejunum and a gastroenterostomy and cholecystoenterostomy performed following resection of the tumor. The patient subsequently died of a recurrence of the tumor and autopsy confirmed the diagnosis of carcinoma of the pancreas. Two months after operation the secretin test was repeated and a definite response to secretin was obtained. Since the tube was introduced through a gastroenterostomy opening, contamination with the gastric contents probably explains the low bicarbonate values but a definite increase in volume occurred and the enzyme content was considerable. Results of the tests were as follows:

	Pre-operative	Post-operative
Volume.....	501 cc.	118.5 cc.
Bicarbonate		
Maximum concentration...	96	16
Total amount.....	382	6.7
Diastase		
Maximum concentration....	1.91	0.47
Total units.....	673	52
Trypsin		
Maximum concentration....	0.26	0.16
Total units.....	115	18
Lipase		
Maximum concentration....	65.5	77.5
Total units.....	31,886	7,111

Postoperative studies of fecal loss of fat and nitrogen on a liberal diet showed a daily fat loss of 31 Gm. and a nitrogen loss of 3.7 Gm. Although these values are definitely abnormal, the loss was considerably less than that obtained by Lake, Cornell and Harrison¹⁴ in another patient on a similar diet with complete absence of pancreatic enzymes following resection of the pancreas head and in whom the fat loss was 70.7 Gm. and the nitrogen loss 6.5 Gm. When

12 Gm. of a potent pancreatic extract was given to this patient daily, the fecal fat loss decreased to 21 Gm. and the nitrogen excretion to 2.7 Gm.; the total weight of the stools also decreased.

CASE 29. A fifty-six year old Arabian cook was admitted to the New York Hospital on December 9, 1941, complaining of gradually increasing epigastric pain of three weeks' duration, which radiated around the left rib border to the left flank, and progressive jaundice, with clay colored stools, for eight days prior to admission.

Physical examination showed jaundice, a palpable liver edge 3 cm. below the costal margin and a markedly enlarged prostate.

Laboratory data revealed the following: The urine showed a faint trace of albumin and 4 plus bile. The stools were semi-formed and clay colored. There was slight anemia, a normal white count and an icteric index of 75. The prothrombin level was 11 per cent; bile was said to be present in the vomitus and a gastro-intestinal series was negative.

On December 17, 1941, an exploratory laparotomy revealed a hard mass in the region of the head of the pancreas which seemed to extend the entire length of the organ. No tumor tissue was found outside of the pancreas. A cholecystogastrostomy was performed. Two weeks after operation bile was present in the eces and the icteric index fell to 9.3.

On January 9, 1942, another exploration was done by another surgeon. The pancreas felt indurated throughout, but since it was uncertain whether this was a tumor or an infection, removal was not attempted. No biopsy was done. The patient was discharged on January 26, 1942, and died at home on August 4, 1942. The course of his disease strongly favors the diagnosis of carcinoma.

<i>Secretin Test</i>	
Volume.....	77 cc.
Highest pH.....	8.1
Bicarbonate	
Highest.....	64
Total in sixty minutes....	34.4
Diastase in sixty minutes....	39 units
Trypsin in sixty minutes....	14 units
Lipase in sixty minutes.....	1878 units

All the values are far below normal levels.

CASE 34. This patient was a sixty-three year

old widow who was admitted to the New York Hospital on January 22, 1942, complaining of dull, boring pain in the left lumbar region for a duration of three months and jaundice for three weeks. The pain was worse at night and was relieved by lying on the left side. She had noted dark urine and light colored stools, and had lost 5 pounds in the previous month.

Physical examination showed moderate jaundice, a palpable liver edge and a firm mass under, but separate, from the liver margin. The Graham test showed no shadow. A gastro-intestinal series showed a disturbed mucosal pattern in the second portion of the duodenum.

Both the feces and urine contained bile until February 6, 1942, when the bile disappeared from the feces. The icteric index was 125 on admission. The prothrombin level was 27 per cent but rose to 97 per cent after two ampules of vitamin K. Serum amylase and lipase were within normal limits.

On February 26, 1942, an exploratory laparotomy was performed. The liver was found to be invaded by a mass of whitish, hard tissue, which also occupied the whole right upper quadrant. It was impossible to tell its point of origin. A biopsy was reported as "metastatic adenocarcinoma, either from the biliary tract or pancreatic tissue." This patient died at home on March 27, 1942. No autopsy was performed. Secretin test gave the following results:

Volume.....	130 cc.
Highest pH.....	8.4
Bicarbonate	
Maximum concentration....	102 milliequivalents
Total output.....	101 N/10 NaHCO ₃
Diastase in 60 minutes.....	62 units
Trypsin in 60 minutes.....	19 units
Lipase in 60 minutes.....	5697 units

The diastase was markedly decreased. The other enzymes were only slightly below normal. The volume and bicarbonate levels were normal.

SUMMARY AND CONCLUSIONS

1. The results of the secretin test are given in eighteen subjects without pancreatic disease and in thirteen subjects with demonstrated disease of the pancreas. The findings agree with those of other investigators and indicate that the secretin

test is a valuable diagnostic procedure when extensive structural changes are present in the pancreas. The earliest and most frequent finding is a decrease in diastase secretion. This was usually the only abnormal finding in chronic pancreatitis.

2. A case of extensive carcinoma of the pancreas with functional hyperactivity is reported. After removal of approximately five-sixths of the organ, the remainder having been implanted into a loop of the jejunum, a definite response to secretin was demonstrated.

3. The composition of pancreatic juice obtained through a fistula was studied before and following the injection of secretin. The composition of this juice was very similar to that of the duodenal contents obtained through the swallowed tube following injection of secretin.

4. The external secretory function of the pancreas was studied at intervals following an attack of acute pancreatic necrosis, and the results showed progressive deterioration.

5. The disappearance of bile from the duodenal contents, following the injection of secretin, appears to be a reliable indication of the presence of a normally functioning gallbladder.

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The Effect of Sodium Salicylate on the Acid-base Balance of the Blood*

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DURING a study of the effect of salicylate therapy in acute rheumatic fever,¹ several patients with high salicylate blood levels were observed to develop tachycardia, hyperpnea and low blood CO₂ content. Probably because of the similarity of such a syndrome with what is seen in diabetic acidosis, salicylates have generally been thought to produce acidosis.

In a recent paper Rapoport and Guest,² after reviewing the literature pointed out the confusion that exists about the blood changes produced by the salicylates and the mechanism of their action on the acid-base balance of the blood. From their own experiments they concluded that salicylates cause "a primary hyperventilation with lowering of the CO₂ tension in the blood, leading to an alkalotic tendency." In the present paper results are reported that were obtained in experiments performed to study the effect of sodium salicylate on the acid-base balance of the blood and the mechanism of its action.

Dogs weighing about 15 Kg. were used. They first received subcutaneously 1.5 to 2 cc. of a 2 per cent solution of morphine sulfate and then intravenously from 1.25 to 1.75 cc. per Kg. of weight of a 20 per cent aqueous solution of sodium barbital. After a period of approximately two hours, changes in respiratory rate were followed by direct observation without recording the depth of respiration. Changes in temperature were read from a rectal thermometer.

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Blood samples were drawn from the femoral artery to follow changes in red cell volume, pH, O₂ and CO₂ content. The red cell volume was determined by the hematocrit method while the CO₂ content and pH values were determined for the most part on whole blood and occasionally on plasma.

The effects of the infusion of saline solution were studied in one control experiment. The dog was anesthetized as described and received intravenously 10 cc. per Kg. of weight of an 0.85 per cent aqueous solution of sodium chloride. The time allowed for the infusion was essentially similar in the control experiment and in the salicylate experiments.

Figure 1 is a graphic representation of the control experiment. It can readily be seen that temperature and respiratory rate as well as pH, oxygen content and CO₂ content of the whole blood changed but little; red cell volume first decreased and then increased.

The effects of the infusion of sodium salicylate were studied in nine experiments. Doses of sodium salicylate ranging from 0.19 Gm. per Kg. to 0.6 Gm. per Kg. were administered, dissolved in distilled water or in an 0.85 per cent aqueous solution of sodium chloride or in a mixture containing half of each. The total volume of the infusion ranged from 5 cc. per Kg. to 11 cc. per Kg. The time allowed for the administration ranged between fifteen and sixty minutes. The blood changes observed in all experiments were qualitatively essentially similar.

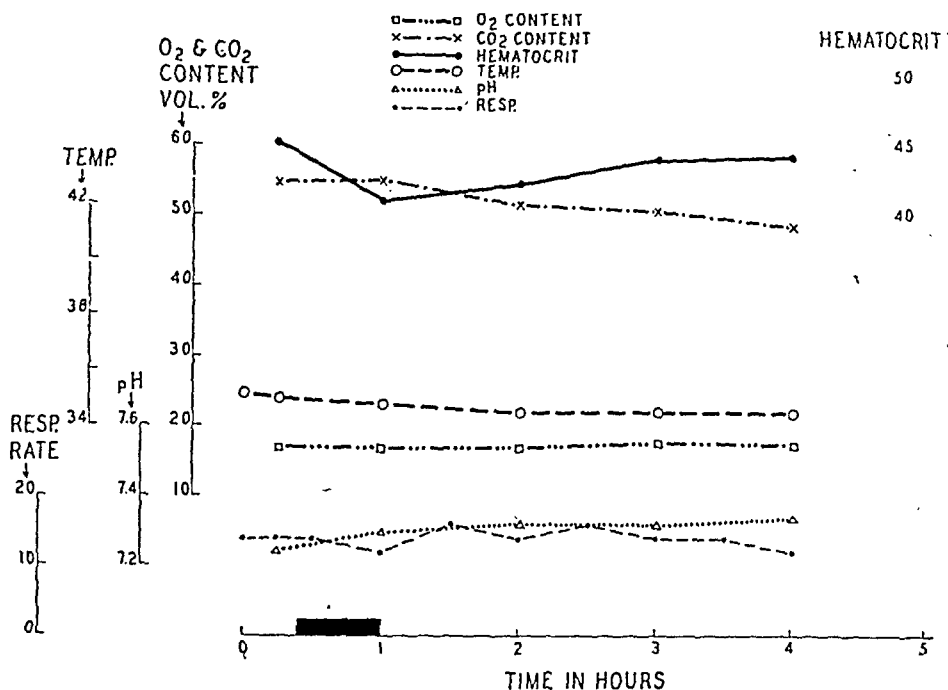


FIG. 1. Effect of the intravenous administration of 10 cc. per Kg. of an 0.85 per cent aqueous solution of sodium chloride on the acid-base balance of a dog under morphine-sodium barbital anesthesia.

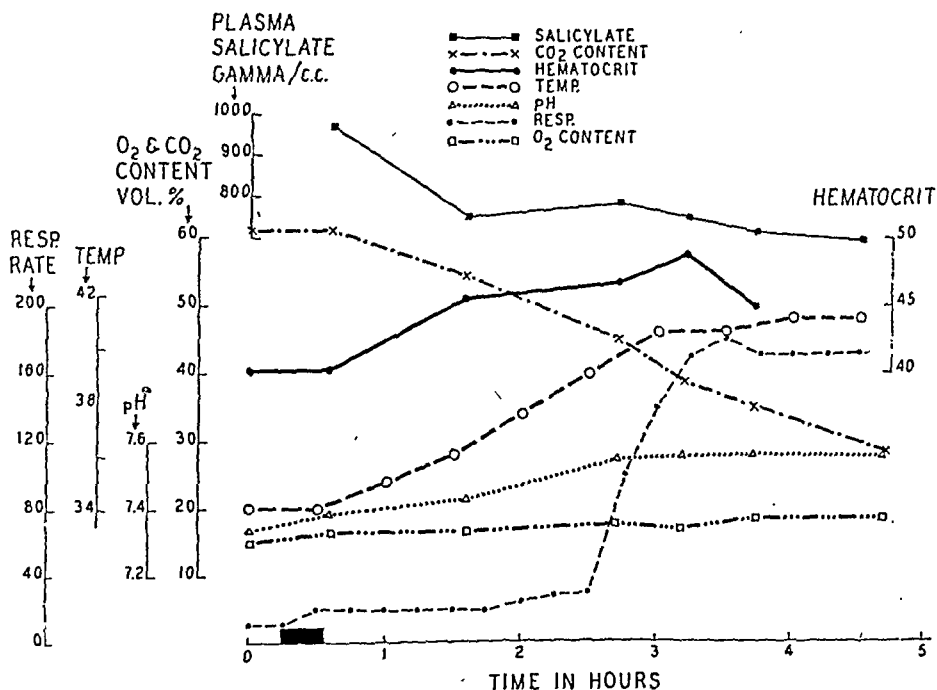


FIG. 2. Effect of the intravenous administration of 9 Gm. of sodium salicylate, dissolved in 100 cc. of an 0.85 per cent sodium chloride solution, on the acid-base balance of a dog weighing 20 Kg. under morphine-sodium barbital anesthesia.

In Figure 2 is pictured one of the nine experiments performed. In this experiment a dog weighing 20 Kg. received 1.75 cc. of a 2 per cent solution of morphine sulfate at 7:50 A.M. Between 8:50 and 9:15 A.M., the dog received intravenously 1.5 cc. per Kg. of a 20 per cent aqueous solution of sodium barbital. Respiratory frequency and temperature were followed from 9:30 A.M. on. At 11:00 A.M. an arterial blood sample was drawn.

Between 11:14 A.M. and 11:33 A.M. the dog received intravenously 9 Gm. of sodium salicylate dissolved in 100 cc. of normal saline. During the infusion no significant changes occurred in pH, CO₂ content, O₂ content or red cell volume of the arterial blood, while the temperature remained unchanged. Soon after, however, the temperature began to rise rapidly and progressively. The respiratory rate remained about the same for approximately one and one-half hours and then increased rapidly. As these changes occurred the CO₂ content of the arterial blood progressively decreased and the pH increased; the red cell volume increased while the oxygen content increased slightly.

COMMENTS

It is quite clear from these experiments that the infusion of sodium salicylate *per se* does not affect the acid-base balance of the blood and that such changes as occur in the acid-base balance are produced through the action of salicylate on respiration. Indeed, the changes brought about in the CO₂ content and pH of the arterial blood can be adequately explained by hyperventilation. Whether sodium salicylate or its products

of degradation act directly on the respiratory center or on nervous structures which in turn stimulate the respiratory center is not apparent. It seems, however, that salicylate can stimulate respiration without affecting the temperature since (1) in six of nine experiments some hyperpnea occurred before any rise in temperature, (2) in all experiments there was no parallelism between increase in temperature and increase in respiratory rate and (3) as pointed out by Guest, Rapoport and Roscoe,³ salicylate alkalosis appears in man after hyperventilation without any rise in temperature.

CONCLUSION

Sodium salicylate does not produce an acidosis but may produce alkalosis. The alkalosis is adequately explained by the respiratory stimulation that sodium salicylate produces. Whether hyperventilation is caused by direct or indirect stimulation of the respiration is not obvious. It is probable that the rise in temperature produced by sodium salicylate is not the only factor responsible for the respiratory stimulation.

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Pulmonary Embolism Caused by Penicillin-Oil-Beeswax*

An Experimental Investigation, with Report of a Near-fatal Case

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THE dangers of the accidental intravenous injection of drugs in oil bases are well known. Although penicillin in an oil-beeswax vehicle has been in clinical use for more than a year, up to the present no report of such a mishap with a penicillin-oil-beeswax preparation has been published. No studies have appeared of the effects of the intravenous injection of the mixture in experimental animals. This communication therefore outlines the consequences of an accidental intravenous injection of a penicillin in oil-beeswax preparation, and summarizes animal experiments in which rabbits were injected intravenously with the same material.

CASE REPORT

L. C., an eighteen-year old colored female, was first seen in the Genitoinfectious Disease Clinic with cutaneous manifestations of secondary syphilis which were positive for *Treponema pallidum* on darkfield examination. A serologic test for syphilis was positive in titer of 40 Kahn units.

The patient was started on a course of daily injections of 600,000 units of penicillin in oil and beeswax. Each cubic centimeter of this material contained 300,000 units of calcium penicillin suspended in peanut oil with 4.8 per cent (w/v) white wax USP. The injections were given in the upper outer quadrant of the buttock in the following manner: A sterile needle without syringe was inserted. After about fifteen

seconds the syringe, which contained previously warmed penicillin-oil-beeswax preparation, was attached. As an additional precaution, the needle was aspirated and only then was the mixture injected.

Eight daily injections were given without difficulty. A few seconds after the ninth injection, however, the patient complained of a peculiar taste in her mouth, "like the smell of penicillin." She coughed a few times, but had no chest pain or dyspnea. After an hour's rest, she felt well and was sent home. The next morning she returned to the clinic. At that time, physical examination of the lungs was normal. Since the patient had no fever and felt well she was given the final injection. That afternoon, however, she began to cough again, and by evening had developed an uncomfortable shortness of breath. During the night she coughed up a considerable quantity of thick, white sputum containing yellow material which "looked like the medicine." She perspired profusely, and toward morning noticed that her sputum was blood-streaked. The shortness of breath became very severe. She returned to the clinic and was admitted to the medical ward.

At that time her temperature was 103°F., pulse 130, respirations 40, and blood pressure 130/70. She weighed 98 pounds (44.5 Kg.). The patient was a slight, well developed colored woman. She sat upright in bed and gasped for breath. She had a paroxysmal, hacking cough, productive of scanty white sputum. Her lips and fingernails were cyanotic, and there was a pronounced inspiratory nasal flare. Excursion

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FIG. 1. First hospital day, patchy densities in peripheral lung fields and reticulated pulmonary pattern; small pleural effusion, right side.

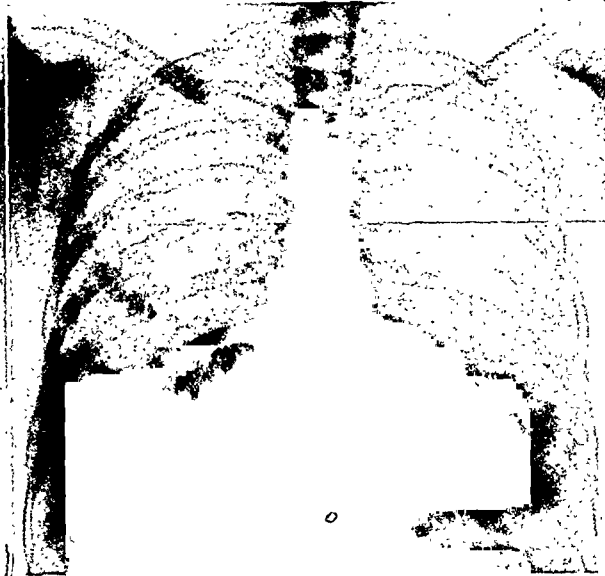


FIG. 2. Fourth hospital day, chest roentgenograms representative for period of second to fourth hospital day; increased pulmonary changes and slight cardiac enlargement; bilateral pleural effusion.

of the chest was limited symmetrically, the respirations being abdominal in character. The percussion note was resonant over the entire chest. On auscultation, a few scattered musical râles were heard posteriorly. The heart was not enlarged and no significant murmurs were heard. The second pulmonic sound was not accentuated, and neck veins were not distended.

The admission white count was 16,150 with 89 per cent polymorphonuclear leukocytes and 1 per cent eosinophiles. She was not anemic, and urine examinations were normal. No fat was found in the urine. Examination of the sputum showed a preponderance of mononuclear cells, many of which had foamy cytoplasm. Attempts to demonstrate sudanophilic fat droplets in the sputum were unsuccessful. No eosinophiles were present in the sputum. The electrocardiogram was normal. A chest roentgenogram (Fig. 1) disclosed numerous, poorly defined, patchy densities throughout both lung fields. These densities measured not more than 1 cm. in diameter and were predominantly localized in the peripheral portions of the lung fields and lung bases. The lung markings showed a streaky accentuation which resulted in a reticulated pulmonary pattern. A small amount of fluid obscured the right costophrenic angle. Fluoroscopically, the heart was normal as to

size and amplitude. Both diaphragms occupied normal positions and showed satisfactory respiratory excursion.

On the first hospital day, the heart was catheterized via the left antecubital vein and the following observations made: right atrial pressure: 7 mm. Hg; right ventricular pressure: 45 mm. Hg; cardiac index (cardiac output in liters per minute per sq. meter of body surface): 2.37; arteriovenous oxygen difference: 9.1 vol. per cent. These determinations demonstrated elevation of the right ventricular pressure, with normal right atrial pressure, decreased cardiac output, and increased arteriovenous oxygen difference. These measurements are compatible with obstruction to the flow of blood through the pulmonary vascular bed. Measurements made on the eighth hospital day by the same methods showed a return to normal in all respects.

During the following days the fever gradually subsided. Dyspnea was severe on the second and third days, as reflected in respiratory rates which rose up to fifty per minute. On the second day, increasing pulmonary changes were noted by roentgenogram. The patchy densities appeared considerably larger and more numerous



FIG. 3. Sixty-eighth day after hospital admission; no residual pulmonary or pleural changes.

and had become confluent in the axillary lung fields. Both costophrenic angles were largely obscured by pleural effusion and the cardiac silhouette had increased slightly in all diameters. The diaphragms were moderately elevated and showed diminished excursion on fluoroscopy.

On the third hospital day, the left pleural space was tapped and about 10 cc. of yellow fluid containing 33,000 cells was removed. Most of these were mononuclear cells, some being small lymphocytes and others larger monocytes and macrophage-like cells, with foamy cytoplasm. Attempts to demonstrate fat in this fluid were unsuccessful. No eosinophiles were found in the pleural fluid.

Chest roentgenograms on the fourth hospital day showed no significant change (Fig. 2); however, by the sixth day, definite evidence of resolution could be seen. At this time the white count was 9,200, of which 31 per cent were eosinophiles. The patient was discharged from the hospital in good condition six days after admission. Roentgenographic studies taken ten days after the accident showed only a few disseminated streaky densities in both lung bases. At this time the pleural effusion had completely disappeared and the heart had returned to normal size. Further examinations on the twentieth, thirty-fourth and sixty-eighth days after hospital admission revealed no abnormal roentgenologic chest findings. (Fig. 3.) The

eosinophile count gradually decreased to 13 per cent forty-four days, and 5 per cent sixty-eight days after admission.

Pulmonary lipid embolism was suspected in this patient when on admission the history was obtained that her symptoms immediately followed the ninth injection of penicillin-oil-beeswax. It was believed, however, that the patient's symptoms were unusually severe, considering that only at most 2 cc. of lipid material could have been injected intravenously. Reports in the literature show that relatively large amounts of oil can enter a vein without producing untoward symptoms.^{1,2} The following case serves to illustrate this point:

In the course of a retrograde urethrogram in a thirty-nine-year old colored man with urethral stricture, large amounts of radiopaque oil were noted in the corpora cavernosa. Ten hours later, no contrast medium remained in the corpora cavernosa, while the lung fields were diffusely mottled with the opaque material, producing a granular pulmonary pattern. At no time did the patient have respiratory symptoms.

The difference in the clinical picture of these two patients was impressive. Both had

accidentally received lipid material intravenously. The first patient could not have received more than 2 cc. of penicillin in oil-beeswax, yet she showed a severe reaction, while the introduction of approximately 5 to 6 cc. of radiopaque oil* into the venous system of the second patient produced no symptoms whatsoever. Experiments were carried out to see if lesions could be produced which might explain the severity of the clinical picture seen in the first patient.

EXPERIMENTAL STUDIES

Method. Different groups of adult rabbits were injected intravenously with 0.05 cc./Kg. of the following preparations:

1. A commercial preparation of penicillin in peanut oil-beeswax (Bristol Laboratories).
2. Peanut oil-beeswax (4.8 per cent white wax U.S.P.†) without penicillin.
3. Peanut oil containing 0.29 per cent mineral oil (w./v). This amount of mineral oil is equivalent to the amount of paraffin hydrocarbons present in 4.8 per cent white wax.
4. Peanut oil alone.
5. An aqueous solution of penicillin, containing 300,000 units per cc. This is the concentration of penicillin present in the commercial preparation.

All animals survived the experiment and did not appear to be ill at its termination. Animals of each group were sacrificed by air embolism five minutes, twenty-four, forty-eight and seventy-two hours after injection. In another set of rabbits, the lethal dose of the oil-beeswax mixture was compared to the lethal dose of peanut oil alone.

Autopsy was performed immediately and the lungs removed. One lung from each animal was fixed in Zenker's fluid with 5

* Iodochloral, Searle, consists of 27 per cent iodine and 7.5 per cent chlorine in organic combination with peanut oil.

† Supplied through the courtesy of the Bristol Laboratories, Syracuse, New York.

per cent glacial acetic acid, and the other lung in a solution of formaldehyde (10 per cent of the U.S.P. concentration). Multiple blocks representing all lobes of each lung were taken and stained with phloxine-methylene blue, Weigert's fibrin stain and with the Ziehl-Neelsen carbol fuchsin stain for the demonstration of acid-fast material. Frozen sections of comparable areas were made from the formalin-fixed tissue and stained with Herxheimer's scarlet red, Nile blue sulfate, and Fischler's method for fatty acid crystals and soaps. Blocks taken from the lungs of the animals injected with the oil-mineral oil mixture were stained for the demonstration of tissue lipase according to the method of Gomori.³

In certain animals, blood was drawn from the heart before injection and at the time of sacrifice for determination of blood lipase levels.⁴ Lungs of animals sacrificed at intervals of five minutes, twenty-four hours and forty-eight hours after injection of the test substance were analyzed chemically for total fat, neutral fat and free fatty acids.⁵

RESULTS

Determination of Lethal Dose. The LD50 of peanut oil-beeswax or of penicillin-peanut oil-beeswax administered intravenously to rabbits was found to be 0.27 cc./Kg. The LD50 of peanut oil alone was 0.75 cc./Kg. (Table I.) Calculations of LD50 were performed by the method of Reed and Muench.⁶ The determination was read at the end of three days. In general, animals receiving fatal doses of peanut oil alone showed signs of cerebral involvement, such as nystagmus, convulsions and irregular slow respirations, while animals injected with lethal doses of peanut oil-beeswax died with pulmonary edema without evidence of peripheral emboli.

Histologic Findings. The histologic findings are identical in the seven animals injected with penicillin in peanut oil-beeswax

(group 1) and in the nine rabbits injected with oil-beeswax mixture alone (group 2). The lungs of the animals sacrificed five minutes after injection show moderately numerous small areas of recent hemorrhage and edema in the alveoli. (Fig. 4.) Many of

TABLE I
LETHAL DOSE ESTIMATION

Oil-Beeswax			Peanut Oil Alone		
Dose cc./Kg.	No. of Animals		Dose cc./Kg.	No. of Animals	
	In-jected	Surviving 3 Days		In-jected	Surviving 3 Days
0.005	6	6	0.005	4	4
0.25	3	3	0.4	2	2
0.27	5	3	0.6	2	1
0.30	3	1	0.8	4	2
0.37	1	0	1.0	1	0
0.42	1	0	1.18	1	0

LD50 oil-beeswax: 0.270 cc./Kg.
LD50 oil alone: 0.747 cc./Kg.

these areas are found near arteries of varying caliber. No appreciable cellular reaction accompanies these hemorrhages. Fat stains reveal large masses of lipid material in a number of medium-sized and large branches of the pulmonary artery. Segments of capillaries in the alveolar walls are similarly obstructed by lipid which forms the center of the hemorrhages.

In animals sacrificed twenty-four hours after injection, hemorrhages are still present. These are now attended by a fair degree of cellular infiltration consisting of numerous heterophiles and some mononuclear cells and lymphocytes. The periphery of the lesions shows edema and congestion. The lesions are moderately numerous and are found scattered throughout the sections. Some medium-sized and large arteries show recent thrombi which have elicited endothelial proliferation. The adventitia of the vessels displays marked cellular infiltration

which is similar to that encountered in the areas of hemorrhage. This infiltration often extends into the adjacent alveoli. In some instances, early granulomatous foci are seen. In the hemorrhagic areas fat stains reveal lipid masses within the capillaries of the alveolar septa which are undergoing necrosis. The same lipid material is also found in the thrombi of the larger vessels. Large mononuclear cells begin to invade the lipid and often show small phagocytized fat globules. At this stage fibroblastic proliferation is inconspicuous around the hemorrhages or thrombosed blood vessels.

Granulomatous lesions predominate in the lungs of animals sacrificed forty-eight hours after injection. Most of the lesions are ill-defined but some are already fairly well demarcated. These granulomas form in the areas of hemorrhage and are also found around the thrombosed vessels where they extend into the adventitia. The core of the granulomas consists of one or several masses of lipid material surrounded by a few giant cells, large mononuclear cells and lymphocytes, as well as quite numerous heterophiles and occasional eosinophiles. At this stage, early proliferation of fibroblasts is noted. The lipid material in the capillaries and larger vessels is undergoing further fragmentation and phagocytosis. The thrombi in the larger vessels display more advanced endothelial proliferation and also beginning organization. Occasional areas of hemorrhage are still present throughout the parenchyma.

A similar picture is seen in the lungs of animals sacrificed seventy-two hours after injection. Here the organization of the thrombi in the large blood vessels is quite advanced. (Fig. 5.) The granulomas are now well defined, contain prominent large multinucleated giant cells and consist chiefly of large mononuclear cells, some lymphocytes, occasional eosinophiles and rare heterophiles. (Fig. 6.) Distinct fibroblastic

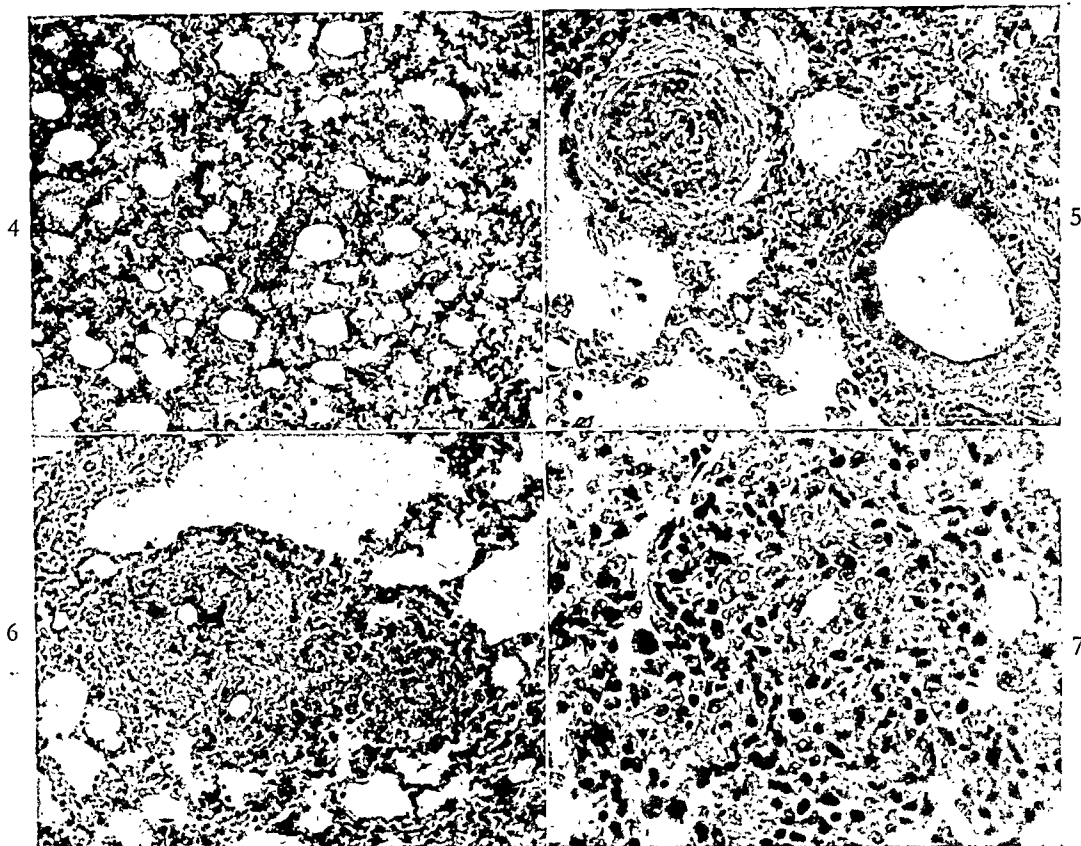


FIG. 4. Rabbit injected with peanut oil-beeswax and sacrificed after five minutes. There is marked patchy edema with slight recent hemorrhage; phloxine-methylene blue. $\times 80$.

FIG. 5. Rabbit injected with peanut oil-beeswax and sacrificed after three days. A large branch of the pulmonary artery is obstructed by a thrombus undergoing organization; phloxine-methylene blue. $\times 120$.

FIG. 6. Rabbit injected with penicillin in peanut oil-beeswax and sacrificed after three days. There are several large and confluent granulomas surrounded by marked cellular reaction (compare with Figs. 8 and 10); phloxine-methylene blue. $\times 80$.

FIG. 7. Granuloma produced by penicillin in peanut oil-beeswax after three days. The space in the center is a mass of lipoid surrounded by a marked chronic inflammatory cell reaction which includes proliferating fibroblasts (compare with Figs. 9 and 11); phloxine-methylene blue. $\times 330$.

proliferation is seen at the periphery of the lesion. (Fig. 7.)

The findings in the lungs of the four animals injected with the peanut oil—mineral oil mixture (group 3) resemble those which have already been described. The granulomas are similar in distribution, size, and cellular components and also show distinct fibrosis. (Figs. 8 and 9.) There is, however, a difference in the size of the arteries which are thrombosed. The large branches of the pulmonary artery are not

involved and thrombi are found only in vessels of smaller caliber.

Nine rabbits were injected with peanut oil alone (group 4). The lungs of the animals sacrificed five minutes after injection show nothing of note with ordinary stains. Fat stains reveal lipoid masses in the capillaries of many alveoli but only a few small arteries are involved.

After twenty-four hours, a fair number of small early granulomas are seen in the alveolar septa and around the few larger

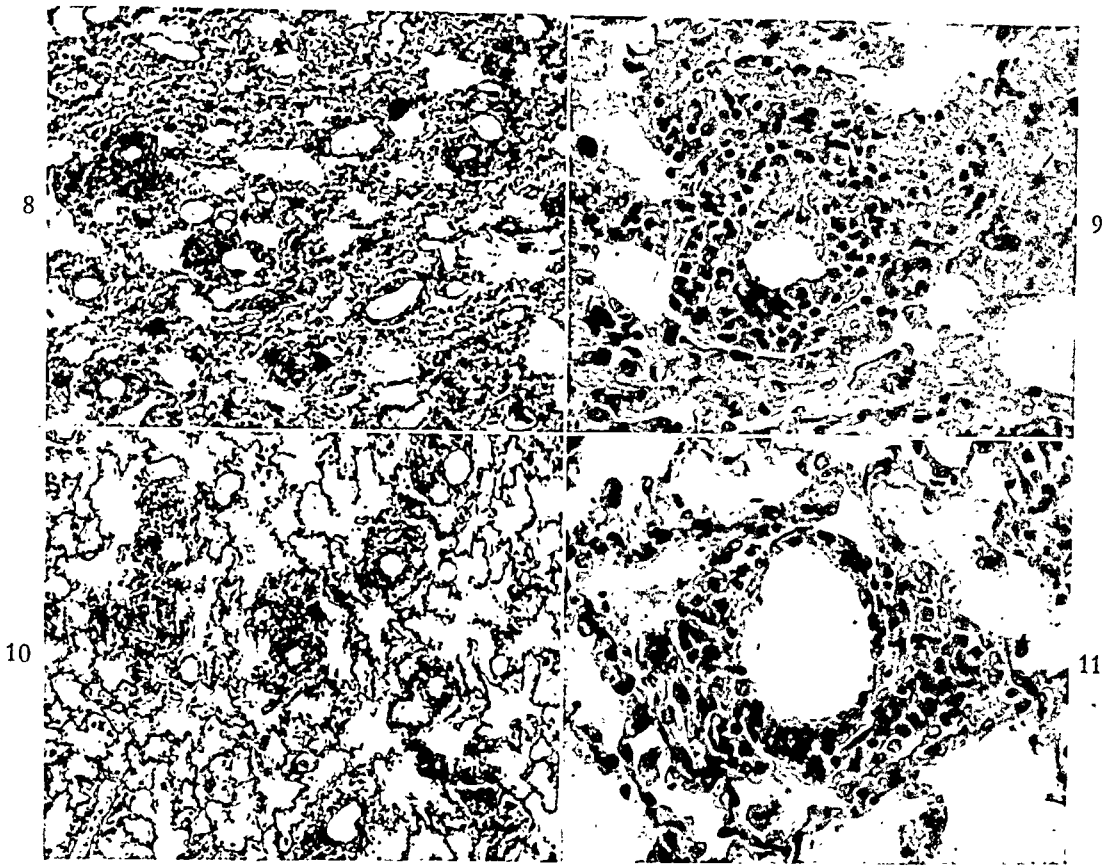


FIG. 8. Rabbit injected with peanut oil-mineral oil and sacrificed after three days. These granulomas are small but tend to be confluent (compare with Figs. 6 and 10); phloxine-methylene blue. $\times 80$.

FIG. 9. Granuloma produced by peanut oil-mineral oil after three days. The central space is a mass of lipoid surrounded by a reaction similar in intensity and cellular components to the reaction produced by penicillin in peanut oil-beeswax (compare with Figs. 7 and 11); phloxine-methylene blue. $\times 330$.

FIG. 10. Rabbit injected with peanut oil alone and sacrificed after three days. The granulomas, like those produced by peanut oil-mineral oil, are small but show less reaction (compare with Figs. 6 and 8); phloxine-methylene blue. $\times 80$.

FIG. 11. Granuloma produced by peanut oil alone after three days. The large central space is a mass of lipoid surrounded by a comparatively slight cellular reaction without appreciable proliferation of fibroblasts (compare with Figs. 7 and 9); phloxine-methylene blue. $\times 330$.

vessels which are involved. The cellular infiltration consists chiefly of heterophiles and some large mononuclear cells and lymphocytes. This infiltration involves the adjacent alveoli. Fat stains show fragmentation and phagocytosis of the lipoid material.

After forty-eight hours the granulomas are well defined and consist mainly of large mononuclear cells and lymphocytes, as well as some multinucleated giant cells. Even after seventy-two hours the granulomas in these animals are smaller than

those in the other series. (Fig. 10.) A slight degree of fibroblastic proliferation is seen. The degree of connective tissue response is less marked in granulomas produced by peanut oil than in lesions of similar size and location produced by the other lipoid substances and after seventy-two hours the fibrosis is not appreciably more marked. (Fig. 11.) Only a few vessels larger than capillaries are involved and those are small arteries.

The various fat stains were positive in

demonstrating the presence of lipoid but were entirely inconclusive as to the proportion of free fatty acids.

The lungs of the animals injected with an aqueous solution of penicillin (group 5) and sacrificed after five minutes and three days showed nothing remarkable.

Chemical Analyses. The histochemical demonstration of lipase in the lungs of the animals injected with peanut oil-mineral oil (group 3) shows small amounts of enzyme in the lesions of twenty-four hours' duration. After forty-eight hours, large amounts of lipase are found while after seventy-two hours the amount of enzyme in the lesions is markedly decreased. The enzyme is seen only in the large mononuclear cells and giant cells of the lesions. In all sections the bronchial epithelium showed the normal positive reaction for the enzyme.

Assays of lungs for fat and fatty acids failed to reveal any increase of the fatty acid content of rabbit lungs twenty-four and forty-eight hours after injection of oil or oil-beeswax. No demonstrable change occurred in the concentration of blood lipase during the course of the experiments.

COMMENTS

The difference in the viscosity of penicillin in peanut oil-beeswax and peanut oil alone is obvious. The oil-beeswax mixture is solid at room temperature and will barely flow at body temperature. Peanut oil is fluid at room temperature. The addition of the small amount of mineral oil involved in these experiments does not appreciably alter its viscosity. The difference in fluidity is reflected in the results of the animal experiments. Sections of the lungs show that the peanut oil and peanut oil-mineral oil pass through the larger vessels and are trapped by the capillaries; on the other hand, most of the oil-wax mixture is arrested in the larger branches of the pulmonary artery. Penicillin does not appear to influ-

ence the location of the emboli. The tendency of the viscous oil-beeswax mixture to be trapped by the larger arteries may in part account for the severity of symptoms in the first case. The quantity of oil-beeswax injected was small; but since it was arrested in the larger vessels, it obstructed the blood supply to a relatively large portion of the lung. In the second case, the oil was dispersed into the pulmonary capillary bed. Since the total diameter of the pulmonary capillary bed is far greater than that of the large arteries, the oil obstructed the blood flow to a relatively insignificant amount of pulmonary tissue, and no symptoms resulted.

The difference in reaction to peanut oil-beeswax and to peanut oil alone does not appear to be confined to purely mechanical factors. The cellular reaction to the oil-beeswax mixture appears to be more intense than that to peanut oil alone, and is associated with an appreciable amount of fibrous tissue proliferation. A comparison of lesions of similar size and location shows that the connective tissue reaction is inconspicuous in the lesions produced by peanut oil alone. This difference suggests a chemical factor. The greater degree of reaction in the lesions produced by the peanut oil-beeswax mixture may be related to the chemical composition of the beeswax. White wax, USP, is a mixture of many substances, which include polyhydric alcohols, long-chain fatty acids and cyclic compounds. It also contains approximately 6 per cent paraffin hydrocarbons.⁷ The addition of paraffin hydrocarbon, in the form of mineral oil, to peanut oil, produced granulomas quite similar in cytology to those caused by the oil-beeswax mixture but involving small arterioles and capillaries. This finding suggests that the difference in the tissue response between the granulomas produced by peanut oil and by peanut oil-beeswax may be due to the small amounts of paraffin hydrocarbon present in the beeswax. The

histologic pattern of the granuloma produced by oil-beeswax resembles that found in lipoid pneumonia.

The comparison of the LD50 of peanut oil-beeswax and oil alone emphasizes the relative toxicity of the two substances. It was found that the preparation containing beeswax was 2.8 times as toxic as peanut oil alone.

Several observers have remarked upon the latent period which may be found between the occurrence of pulmonary fat embolism and the development of severe symptoms.^{8,9} Our patient was relatively asymptomatic immediately after the offending injection. After twenty-four hours, however, she began to develop pulmonary distress which became progressively more severe until it reached a peak on the second hospital day (fourth day of present illness). Harris and co-workers¹⁰ have postulated that the late appearance of symptoms is the result of hydrolysis of the fat particles with release of free fatty acids. It is known that the severity of the tissue reaction to lipoids increases with their free fatty acid content. An appreciable increase in lipase activity was found in the granulomas produced by the oil-mineral oil mixture after forty-eight hours. The delay in the development of maximal lipase activity correlates roughly with the appearance of the granulomas in the experimental animals. In an analogous fashion, the roentgenographic findings in our patient indicated a progression of the pulmonary involvement, reaching its maximum between the second and fourth hospital days.

A comparison of clinical and roentgenographic findings with the experimental data might be interpreted as offering support for the concept that the increase of the patient's symptoms is related to the enzymatic release of irritating free fatty acids from the relatively bland neutral fat.⁴ Other histologic technics, as well as chemical analyses were

inconclusive, possibly because the methods at our disposal were not sufficiently sensitive.

The first patient developed a marked eosinophilia during her stay in the hospital. There were no cutaneous manifestations of allergy, and no ova of intestinal parasites were found. No eosinophiles were found in the sputum or pleural exudate. Subsequent investigation of a large number of patients receiving penicillin in oil-beeswax intramuscularly in the Genitoinfectious Disease Clinic revealed that approximately 10 per cent of all patients receiving the preparation have elevated eosinophile counts, ranging from 10 to 30 per cent.¹¹ We believe that the eosinophilia in our patient is not indicative of the presence of allergic disease. The coincidence of pulmonary disease and eosinophilia raises the question of Loeffler's syndrome. The roentgenographic findings, severity of the disease, and spontaneous rapid resolution in a period of less than two weeks are incompatible with this diagnosis.

The roentgenographic findings are of interest because the symmetrical, peripheral distribution of the opacities is similar to that seen in protracted types of hematogenous tuberculosis and in diffuse pulmonary carcinomatosis. This similarity suggests additional evidence that our patient's symptoms arose following multiple pulmonary emboli.

These studies indicate that every precaution should be taken to prevent the intravenous administration of oil-beeswax preparations. The danger involved is greater than when oil alone is involved. If an oil-beeswax mixture is injected intravenously, the patient should be kept under close observation. For twenty-four hours after the accident, our first patient gave no indication of the severity of the impending reaction. At the time of admission, thirty-six hours after the injection, roentgenograms of the chest showed extensive involvement of the lung. Clinically and roentgenologically the pulmonary findings were most pronounced

on the second and third hospital days. There was a rapid clinical improvement thereafter, though the roentgenograms showed a somewhat delayed resolution of the pathologic process. It is noteworthy that roentgenologic and clinical examinations twenty days after the injection showed no residual pulmonary changes. It therefore seems advisable to hospitalize patients suspected of having had an oil-beeswax mixture injected intravenously. Such patients should be observed for at least three days before the possibility of a severe late reaction is discarded.

CONCLUSIONS

A case is reported of a severe reaction to the accidental intravenous administration of penicillin in oil-beeswax. Animal experiments were done which indicated that the severity of the reaction was due to two factors: first, the viscosity of the oil-beeswax mixture which caused it to block large branches of the pulmonary artery, and second, the severe inflammatory reaction elicited by the beeswax.

Evidence was obtained which suggested that the severity of the inflammation may be due to the chemical composition of the wax. Attempts to correlate the morphology of the lesions in experimental animals with

the chemical demonstration of free fatty acids in tissues were inconclusive.

The importance of precaution against intravenous injection of penicillin-oil-beeswax is stressed.

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The Electrocardiogram in Lupus Erythematosus Disseminatus*

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THE involvement of the heart in disseminated lupus erythematosus is well known. There may be vegetations of the endocardium, first described by Libman and Sacks.¹ The myocardium is often the seat of focal inflammation and the pericardium may become thickened and adherent with resulting synechiae cordis or even complete obliteration of the pericardial sac. Laipply and Longley² are of the opinion that the pathologic picture is not definite but Klemperer, Pollack and Baehr³ believe that the changes, wherever they occur in the body, are due to collagenous proliferation and degeneration.

It is to be expected that such marked anatomic changes in the heart would have an effect on the electrocardiogram. The present study was made to review the literature on this subject and to add the observations in eight additional cases of disseminated lupus erythematosus proved by post mortem examination. The authors have been unable to find any articles dealing with the electrocardiographic changes alone but there are numerous references in the literature to the changes in the electrocardiogram in case reports of disseminated lupus. Baehr,⁴ in his account of the disease in Cecil's Textbook of Medicine, states: "The electrocardiogram reveals no characteristic changes as a rule except for low voltage." In a brief review of the literature of lupus erythematosus disseminatus Cluxton and Krause⁵ make the same statement.

In their case reports an electrocardiogram taken on each of two (out of four) cases was normal in one instance and in the other showed "notching of T in Lead IV." Isolated case reports⁶ have noted low or inverted T waves in Leads I, II and IV, increased P-R interval and increase in left axis deviation. Bunim⁷ reported low voltage and premature ventricular and "His bundle" contractions; in another case report the Reifenshteins⁸ also noted low voltage. In both of these instances postmortem examination revealed chronic pericarditis with fibrous adhesions between visceral and parietal pericardium. This was the only cardiac abnormality in one case; the other had, in addition, vegetative endocarditis. Baehr, Klemperer and Schiffrin⁹ found that "the only abnormality characteristic of all electrocardiograms was low voltage" but do not state whether or not electrocardiograms were taken in all instances.

In this report the electrocardiograms of eight cases of lupus erythematosus disseminatus were analyzed.

FINDINGS

1. The electrocardiograms of four patients were normal. In one case the record was made three years and nine months before death but in the other three instances the records were made fifty-five, thirty and thirteen days before death. At postmortem examination one heart was normal; one

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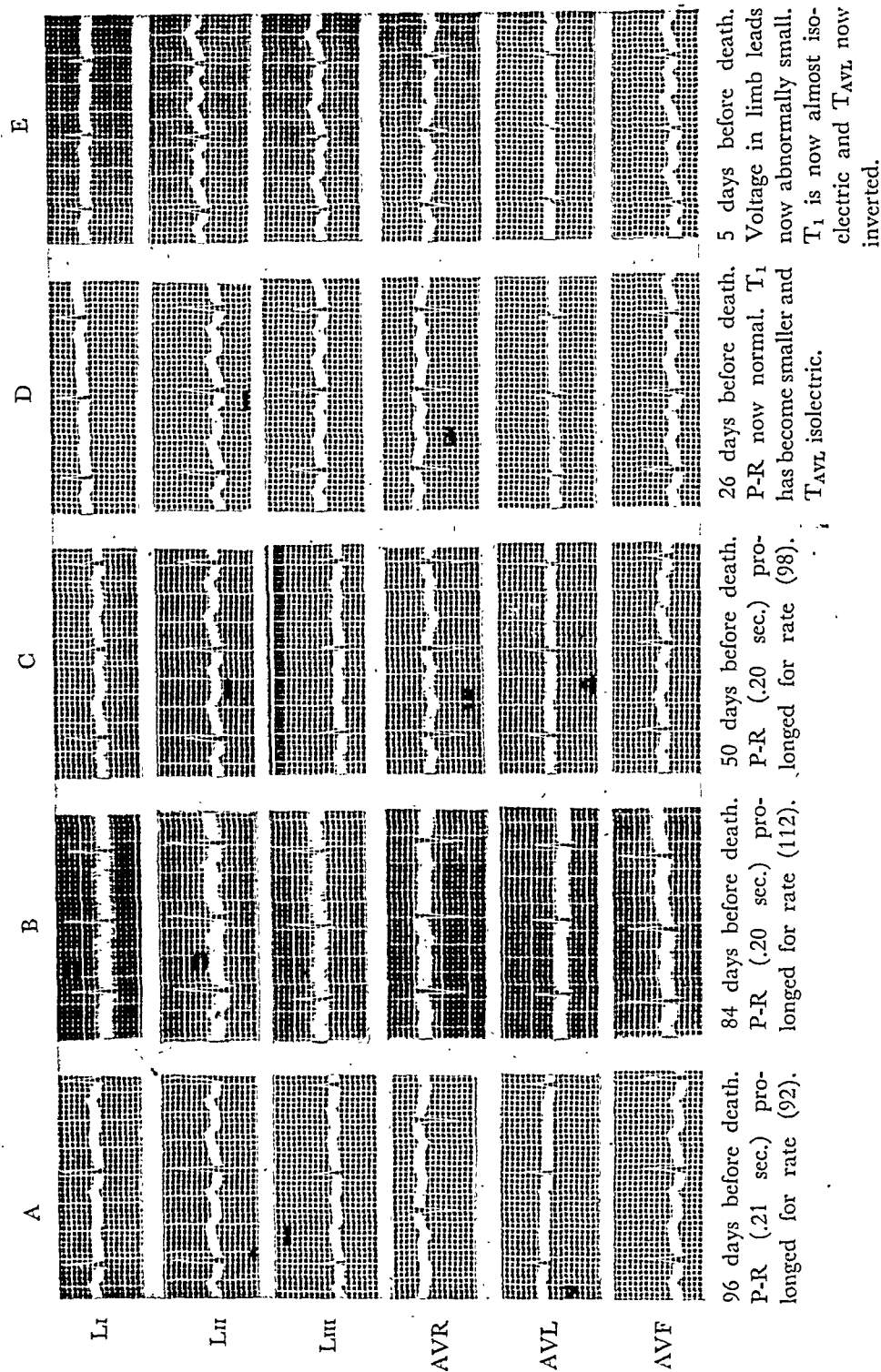


FIG. 1. O. N., female; anatomical diagnoses (cardiac); healed verrucose endocarditis of mitral and tricuspid valves.

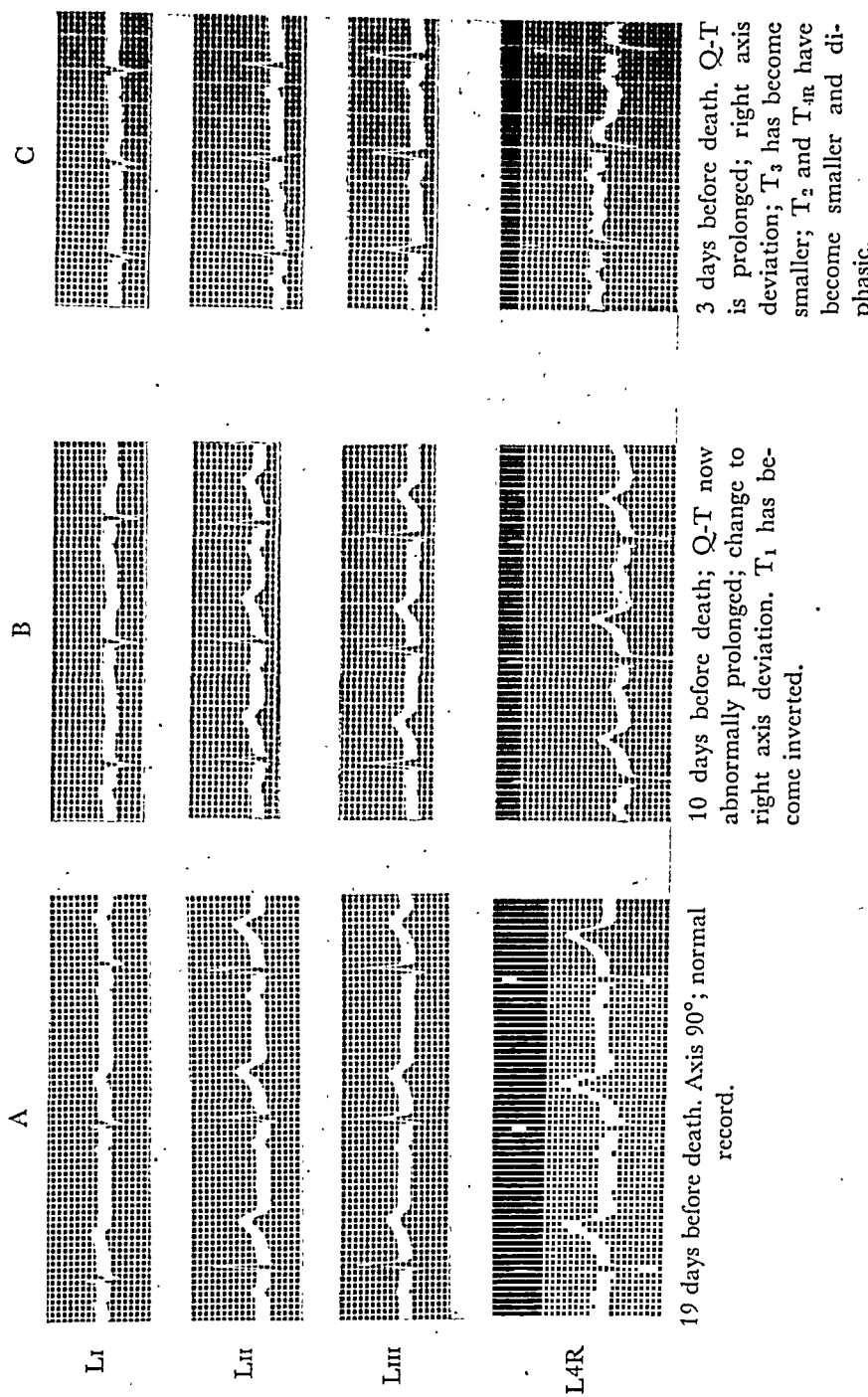


FIG. 2. T. P., male; anatomical diagnoses (cardiac); acute vegetative endocarditis of all four valves; subacute myocarditis, hydropericardium (450 cc.), hypertrophy and dilatation of the heart (415 Gm.).

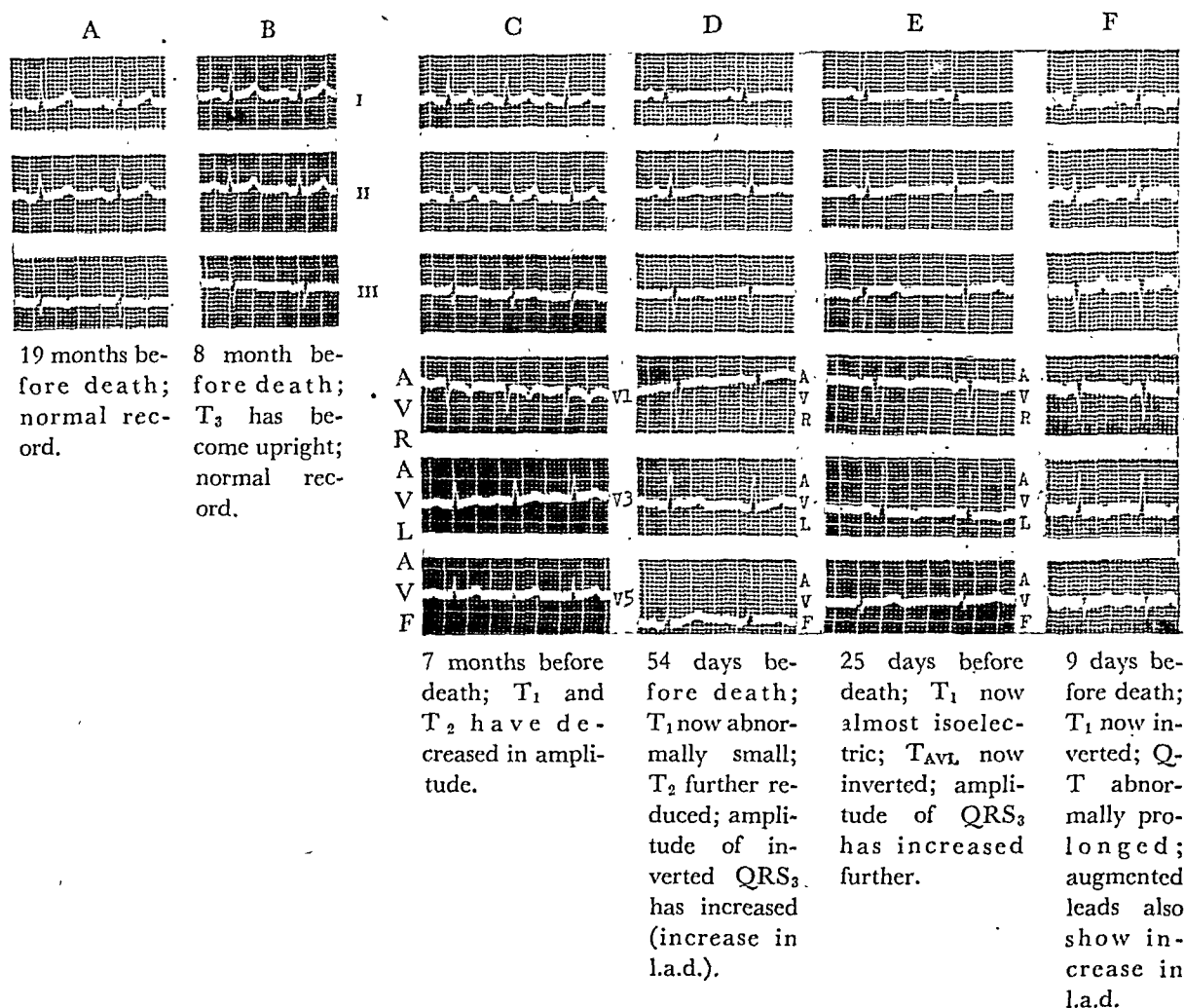


FIG. 3. C. L., female; anatomical diagnoses (cardiac); miliary abscesses of epicardium and myocardium, hydropericardium (300 cc.), cardiac hypertrophy (380 Gm., expected weight 290 Gm.).

had focal myocarditis, endocarditis and mitral valvulitis; one had synechiae cordis and mitral valvulitis; one had synechiae cordis, myocarditis and mitral and aortic valvulitis. (Table II.)

2. In two patients the electrocardiograms showed abnormally low voltage (amplitude of QRS less than 5 mm. in all limb leads). One patient had complete obliteration of the pericardial space by fibrous adhesions, plus mitral and pulmonary valvulitis. Low voltage was evident ten months before death. The other had healed verrucous endocarditis of the mitral and tricuspid valves; the pericardium, myocardium and the lin-

ing endocardium were normal. In this patient low voltage was first found five days before death.

3. Progressive T wave changes occurred in the electrocardiograms of three patients. (Figs. 1, 2, and 3.) The first (Fig. 1) had healed mitral and tricuspid valvulitis; the lining endocardium, myocardium and pericardium were normal. The second (Fig. 2) had acute vegetative endocarditis of all four valves, subacute myocarditis, hydropericardium (450 cc.) and cardiac hypertrophy and dilatation (415 Gm.). The third (Fig. 3) showed miliary abscesses of

the epicardium and myocardium, hydropericardium (300 cc.) and cardiac hypertrophy (380 Gm.).

4. Axis change was seen in two patients. In one the axis shifted from 90° to abnormal right axis deviation. In the other a slight

TABLE I

Case	Re-cord	R-R	Q-T	K	Expected K	
					Normal	Upper Limit of Normal
O. N. ♀	1	.66	.35	.432	.415	.456
	2	.54	.32	.436	.415	.456
	3	.62	.34	.432	.415	.456
	4	.56	.31	.415	.415	.456
	5	.52	.30	.416	.415	.456
M. R. ♀		.58	.30	.394	.415	.456
V. C. ♀		.72	.33	.389	.415	.456
S. K. ♀		.60	.35	.452	.415	.456
E. B. ♀		.80	.39	.436	.415	.456
T. P. ♂	1	.91	.41	.419	.397	.433
	2	.68	.38	.461	.397	.433
	3	.56	.35	.468	.397	.433
M. S. ♀		.53	.28	.385	.415	.456
C. L. ♀	1	.59	.32	.417	.415	.456
	2	.69	.36	.434	.415	.456
	3	.52	.29	.402	.415	.456
	4	.69	.36	.434	.415	.456
	5	.83	.40	.440	.415	.456
	6	.56	.36	.482	.415	.456

left axis deviation became more marked. (Figs. 2 and 3.)

5. P-R was prolonged in one patient. (Fig. 1.)

6. The Q-T interval was prolonged beyond the upper limit of normal in two patients. In three other patients Q-T fell within the normal range but was longer than average. This marked tendency toward prolongation of Q-T, definitely abnormal in two patients, can be readily seen in Table I. In this table "K" was calculated

from the formula $K = \frac{Q-T}{\sqrt{R-R}}$. The "Normal" and "Upper Limit of Normal"

values for expected K are those of Shipley and Halloran.¹⁰

A summary of the electrocardiographic and anatomic findings is seen below, in Table II.

TABLE II

Case	Pathologic Findings	Electrocardiographic Findings
S. K. ♀	Chronic pericarditis with obliteration of pericardial space by fibrous adhesions Chronic mitral and pulmonary valvulitis (undetermined type)	Low voltage
M. R. ♀	Focal myocarditis and necrosis of arterioles Acute mural endocarditis Acute mitral valvulitis	Normal (taken 13 days before death)
V. C. ♀	Normal heart	Normal (taken 55 days before death)
M. S. ♀	Synechiae cordis with complete obliteration of pericardial space. Mild cardiac hypertrophy (500 Gm.) Healed mitral valvulitis	Normal (taken 30 days before death)
E. B. ♀	Synechiae cordis Acute and subacute myocarditis Chronic proliferative and verrucose mitral and aortic valvulitis	Normal (taken 3 years and 9 months before death)
O. N. ♀	Healed verrucose endocarditis of mitral and tricuspid valves	Prolonged P-R interval Low voltage Flattening of T ₁ ; inversion of T _{IVL}
T. P. ♂	Acute vegetative endocarditis of all four valves Subacute myocarditis Hydropericardium (450 cc.) Hypertrophy and dilatation of heart (415 Gm.)	Q-T abnormally prolonged Change to right axis deviation Inversion of T ₁ ; flattening and diphasicity of T ₂ and T _{IVR} ; flattening of T ₃
C. L. ♀ *	Miliary abscesses of epicardium and myocardium Hydropericardium (300 cc.) Cardiac hypertrophy (380 Gm.) Chronic epicarditis	Q-T abnormally prolonged Increase in left axis deviation Inversion of T ₁ ; decrease in amplitude of T ₂ ; change of T ₃ from inverted to upright

* This patient's illness was complicated by terminal pyemia (alpha hemolytic streptococcus and hemolytic staphylococcus).

SUMMARY

Abnormalities of the electrocardiogram in patients with lupus erythematosus disseminatus have been noted by several authors in case reports. These abnormalities have consisted of low voltage, increased P-R interval, increase in left axis deviation, low or inverted T waves and premature beats.

This report presents the electrocardiographic findings in eight autopsied cases of lupus erythematosus disseminatus. All abnormalities noted above were found in this group with the exception of premature beats. In addition, change of axis from normal to right axis deviation occurred. There was also a general tendency toward prolongation of the Q-T interval; in two patients Q-T was abnormally prolonged. Low voltage was not as common as reported in other series.

Electrocardiographic changes were seen as long as ten months before death. In those patients in whom a series of records was obtained the electrocardiograms became progressively and increasingly abnormal. In three of eight patients in whom there was anatomic abnormality of the heart there was no change in the electro-

cardiogram. In all of these, however, there was no series of records; only a single electrocardiogram was available for study.

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Metopon Hydrochloride

Methyldihydromorphinone Hydrochloride

STATEMENT OF COMMITTEE ON DRUG ADDICTION, NATIONAL RESEARCH COUNCIL

IN 1929 with the funds provided by the Rockefeller Foundation, the National Research Council through its Committee on Drug Addiction undertook a coordinated program to study drug addiction and search for a non-addicting analgesic comparable to morphine. The principal participating organizations were the Universities of Virginia and Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics and the Health Department of the State of Massachusetts, which brought together chemical, pharmacological and clinical facilities for the purpose of the study. Metopon is one of the many compounds made and studied in this coordinated effort.

Chemically, metopon is a morphine derivative; pharmacologically it is qualitatively like morphine even to the properties of tolerance and addiction liability. Chemically, metopon differs from morphine in three particulars—one double bond of the phenanthrene nucleus has been reduced by hydrogenation, the alcoholic hydroxyl has been replaced by oxygen and a new substituent, a methyl group, has been attached to the phenanthrene nucleus. Studies made thus far indicate that pharmacologically metopon differs from morphine quantitatively in all of its important actions. Its analgesic effectiveness is at least double and its duration of action is about equal to that of morphine; it is nearly devoid of emetic action; tolerance to it appears to develop more slowly and disappears more quickly and physical dependence builds up more slowly than it does with morphine; ther-

apeutic analgesic doses produce little or no respiratory depression and much less mental dullness than does morphine and it is relatively highly effective by oral administration.

In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients, individuals addicted to morphine and others (terminal malignancies) needing prolonged pain relief but without previous opiate experience. In morphine addicts metopon appears only partially to prevent the impending signs of physical and psychical dependence. In terminal malignancy, administered orally, it gives adequate pain relief with very little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence.

The high analgesic effectiveness of oral doses (with the elimination of the disadvantage to the patient of hypodermic injection), the absence of nausea and vomiting even in patients who vomit with morphine or other derivatives, the absence of mental dullness and the slow development of tolerance and dependence place metopon in a class by itself for the treatment of the chronic suffering of malignancies and it is for that purpose exclusively that it is being manufactured and marketed.

Metopon will be available only in capsule form for oral administration. The capsules will be put up in bottles of one hundred and each capsule will contain 3.0 mg. of metopon hydrochloride. They can be obtained by physicians from only

Sharp & Dohme or Parke, Davis & Co., on a regular official Narcotic Order Form which must be accompanied by a signed statement supplying information as to the number of patients to be treated and the diagnosis on each. The drug will be distributed for no other purpose than oral administration for chronic pain relief in cancer cases.

The dose of metopon hydrochloride is 6.0 to 9.0 mg. (2 or 3 capsules) to be repeated only on recurrence of pain, avoiding regular by-the-clock administration. As with morphine it is most desirable to keep the dose at the lowest level compatible with adequate pain relief, therefore administration should be started with 2 capsules per dose increasing to 3 only if the analgesic effect is insufficient.

Tolerance to any narcotic drug develops more rapidly with excessive dosage and under regular by-the-clock administration. Also as a rule the pain of cancer varies widely in intensity from time to time. Pain, therefore, should be the only guide to time of administration and dosage level. Tolerance to metopon hydrochloride develops slowly. It can be delayed or interrupted entirely by withholding the drug occasionally for twelve hours or for as much of that period as the incidence of pain will permit.

A record card will be sent to each physician for each patient to whom metopon hydrochloride is to be administered. He will be requested to fill out these cards and return them in the addressed return envelope. He must furnish this record of the patient and his use of metopon hydrochloride if he wishes to repeat his order of the drug. The principal object of this detailed report is to check the satisfactory results of metopon hydrochloride administration in general practice. The physician's

cooperation in making it as complete as possible is earnestly solicited.

The limited use of metopon hydrochloride as described above has been recommended by the Drug Addiction Committee of the National Research Council, and the Committee, with the cooperation of the American Cancer Society, will supervise the distribution of the drug. The Committee is composed of William Charles White, Chairman, Washington, D. C.; H. J. Anslinger, Commissioner of Narcotics, United States Treasury Department, Washington, D. C.; Lyndon F. Small, National Institute of Health, Washington, D. C. and Nathan B. Eddy, National Institute of Health, Washington, D. C. Queries and comments on metopon may be directed to Dr. Eddy who will answer them on behalf of the Committee.

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Clinical Syndromes Associated with Gonadal Failure in Men*

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THE testes have two functioning systems, one composed of the interstitial or Leydig cells with internal secretory activity for the elaboration of male sex hormone, testosterone;^{1,2} the other made up of the seminiferous tubules for the production of mature spermatozoa. Although some internal secretory activity begins shortly after birth,³ no apparent spermatogenic function is noted until puberty. At that time, secondary to spontaneous hypophyseal gonadotropic activity,⁴ both testicular systems mature and become active, usually for the remainder of the individual's span.⁵ Either or both testicular functions may fail to achieve normal activity at puberty, or to maintain this level once function has been established. The clinical picture which ensues then depends on the function lost and on the time in relation to maturation.

The establishment and maintenance of adult testicular function depends upon normal genetic, embryologic and physiologic development and upon avoidance of disease or injury to the organ. Any disturbance in the above influences may derange testis function. Such disorders are herein outlined to provide a working etiologic basis of classification for purposes of discussion.

DISORDERS OF THE TESTES

I. Prepuberal, Prior to Sexual Maturation

A. Primary, or in the testes proper

1. Non-destructive

(a) Genetic: defective germ plasm anlage

(1) Eunuchoidism—some cases.

(2) Aplasia testis (?)

(b) Physiologic: hormonal excesses affecting the fetus in utero—pseudohermaphroditism

2. Destructive

(a) Embryologic: disturbances in descent of the testes

(1) Compromise of blood supply with atrophy, aplasia testis (?)

(2) Cryptorchidism

(a) Complete tubule destruction by body heat at puberty

(b) Incomplete interstitial cell function loss

(3) Maldescent of the testes; no function loss other than with cryptorchidism

(b) Pathologic: mumps, malignancy, operation, injury, etc. (See II, A.2.)

B. Secondary, or elsewhere than in the testes

1. Disturbance of the anterior hypophysis proper

(a) Non-destructive

(1) Normal onset of gonadotropic activity as late as sixteen years of age

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- (2) Seasonal inactivity—animals only
- (3) Eunuchoidism—some cases
- (4) Dwarfism (genetic, somatic, vs. hypophyseal origin of this disorder)
- (b) Destructive
 - (1) Adenomas of the anterior hypophysis—usually post-puberal
 - (2) Rathke's pouch cyst or tumor
 - (3) Fröhlich's syndrome
 - (4) Carcinoma, tuberculosis and miscellaneous diseases of the hypophysis

- 2. Disease elsewhere than the hypophysis; interrelationship with anterior hypophyseal function
 - (a) Diabetes mellitus
 - (b) Starvation and inanition
 - (c) Vitamin deficiency, especially thiamin, vitamin A
 - (d) Defective absorption from gastrointestinal tract, as in chronic diarrhea, sprue
 - (e) Chronic renal disease
 - (f) Thyroid disorders
 - (1) Hypothyroidism
 - (2) Hyperthyroidism
 - (g) Adrenal disorders
 - (1) Addison's disease
 - (2) Cushing's syndrome
 - (3) Cortical hyperplasia and adenoma

II. Postpuberal, after Sexual Maturation

A. Primary, or in the testes proper

- 1. Non-destructive
 - (a) Male climacterium
 - (b) Sterility—genetic?
- 2. Destructive
 - (a) Orchitis—usually unilateral
 - (1) Mumps
 - (2) Tuberculosis
 - (3) Lues

- (b) Malignancy—usually unilateral⁶

- (1) Origin in embryonal rest cells
 - (a) Chorionepithelioma
 - (b) Teratoma
- (2) Origin in seminiferous epithelium—seminoma
- (3) Origin in interstitial tissue
 - (a) Adenoma
 - (b) Hyperplasia
- (4) Origin in connective tissue
 - (a) Fibroma
 - (b) Myoma
- (c) Compromise of blood supply, as after hernia repair
- (d) Castration—carcinoma of prostate, etc.
- (e) Injury—avulsion, etc.
- (f) X-radiation
- (g) Chemicals—e.g., alcohol, toxins
- (h) Abnormally high body temperatures

B. Secondary, or elsewhere than in the testes

- 1. Disturbance of the anterior hypophysis proper
 - (a) Non-destructive—? actually occurs
 - (b) Destructive
 - (1) See outline I, B.
 - (2) Aneurysm internal carotid artery
- 2. Disease elsewhere than the hypophysis; interrelationship with anterior hypophyseal function
 - (a) See outline I, B, 2.
 - (b) Estrogen or androgen excess
 - (1) Therapeutic administration
 - (2) Failure of inactivation of endogenous hormone, in liver disease

GONADAL DEVELOPMENT AND DIFFERENTIATION

The testes arise from the genital ridge on either side of the human embryo at the 20 mm. stage, in the seventh week of pregnancy. The cells begin to differentiate into tubule and interstitial cells at this time, although this process may be renewed after birth. Migration of the testes to the scrotum commences at the 41 mm. stage in the third month and descent is completed one to two months after birth.

The differentiation of the gonad into a male or female organ is under genetic or chromosomal control but may be altered by unusual hormonal influence during gestation.⁷ Such hormonal excess may come from the mother, a twin embryo (in the cow), or from the endocrine system of the fetus itself. In the last instance, the fetal overactivity may have been initiated by either of the other two. Pseudohermaphroditism in man is an example of this. The overactivity of the fetal adrenal cortex occasionally continues after birth, as shown by enlarged adrenal cortices⁸ and by an excess excretion of neutral 17-ketosteroids in the urine of the human pseudohermaphrodite. In the chick and the rat, complete alteration of the genital tract so that it has the morphologic structure of the opposite sex has been accomplished by the injection of steroid hormones during gestation.⁷ The gonads have been said to be completely reversed in some experiments.⁹

Failure of differentiation of the interstitial or tubule cells can occur even in a normal hormonal environment. A defective germ plasm is postulated as the cause,¹⁰ perhaps secondary to bad nutrition or disease of the mother during pregnancy.¹¹ Sterility or eunuchoidism may thus result; though the mechanism has not been fully established.

If adequate gonadal differentiation from the genital ridge has taken place, the descent

to the scrotum offers the next threat to function and development. The anatomy and consequences of deranged descent are well understood and need no review. Bilateral cryptorchidism, or failure of the testes to emerge from the abdominal cavity, results in, early, probably irreversible disappearance of spermatogenesis, if uncorrected, shortly after puberty has begun. This results from the higher temperature within the body as compared with that of the scrotal sac. Interstitial cell, or internal secretory activity, however, may persist for a longer period before failing. Emergence of the testes through the internal ring but failure to complete descent because of mechanical obstruction generally causes no disturbance in testicular function. The retractile testis descends at puberty and functions normally if left alone.

Occasionally, exploration of the cryptorchid individual reveals the presence of no testicular tissue, i.e., aplasia testis. A possible explanation for this defect is that the germ plasm is faulty and fails to provide an anlage for testicular differentiation. Another possibility is that the embryonic blood supply of the testes may have been compromised during descent, with complete testicular atrophy as a result.

Following normal development and descent of the testes, physiological control of testicular function is established through the gonadotropic activity of the anterior hypophysis. The testes remain small and immature until puberty. At this time, spontaneous hypophyseal activity occurs, gonadotropic hormone is secreted and causes growth and activity of both systems of the testis. This so-called gonadotropic hormone may be two distinct substances, one of which activates the interstitial cells and is probably identical with the luteinizing hormone of the female,¹² the other stimulates the tubule cells and is probably the same as the follicle stimulating hormone of the opposite sex.¹³

The individual identity of the two hormones in either sex is not yet universally accepted.

Gonadal failure in the young, without testicular destruction, obviously cannot be diagnosed until after puberty is normally initiated, since the infantile status is the norm before this event. Puberty may not commence until the sixteenth year of age in some healthy individuals, with an average age of onset at thirteen.¹⁴ It is thus suggested that the diagnosis of gonadal failure should not be made before the seventeenth year of age unless cryptorchidism is present, or the increased amounts of pituitary gonadotropin associated with castration are found in the urine.¹⁵ An understanding of the age limits of puberty will save many normal subjects, especially when somewhat obese, from false diagnosis and unnecessary treatment for testicular failure, e.g., eunuchoidism or Fröhlich's syndrome.

On the other hand, lack of pituitary function can prevent the onset of puberty. It is now suspected that the gonadotropic activity of the anterior hypophysis may fail to set in spontaneously at puberty and this is thought to be the cause of some cases of eunuchoidism.^{16,17} Gonadotropic failure may result from compression or destruction of the pituitary by tumors, cysts, etc. Finally there may be cessation of pituitary function as the result of systemic disturbances such as inanition, uncontrolled diabetes mellitus, vitamin deficiency, or various diseases. The histological appearance of the gonads in the rat during inanition, for example, may approach that resulting from hypophysectomy, indicating that suppression of anterior hypophyseal gonadotropin output is the probable basis for the change.¹⁸ This concept is strengthened by the response of these atrophied organs to gonadotropin.¹⁹

Spontaneous loss of testis function after puberty is said to occur. This produces the so-called male climacterium with symptomatology similar to that of the female

menopausé. There is some question as to the actual frequency of occurrence of this disturbance, as compared with symptoms due to a neurotic or emotional state at this age.

Destructive lesions of the testes, of course, may cause loss of testicular function at any time but usually after puberty. Tuberculosis, mumps, syphilis and tumors of various types affect the testes, though usually the involvement is unilateral. The remaining normal gonad prevents the appearance of castration symptoms or of sterility. If the remaining gonad is defective, castration symptoms of course, result. Injury with crushing or avulsion, x-radiation in excess, hernia repair with compromise of the cord in the scar and subsequent atrophy of the testes, and castration as for carcinoma of the prostate are other means by which gonadal function may be destroyed.

Persistent therapy with large doses of estrogen or androgen,²⁰ or failure of inactivation of normal amounts of these hormones in liver disease²¹ increases the amount of circulating hormone and so may depress hypophyseal gonadotropin output. Spermatogenesis may be entirely repressed although this suppression is usually reversible on stopping therapy or on correcting the liver disturbance. Failure of internal secretory activity of the testes may result apart from tubule failure after hormone excess. This is not noticed during androgen therapy, due to the similar effects of the administered and endogenous hormones, but may be revealed during estrogen therapy when loss of libido may occur from suppression of hypophyseal secretion, and hence of testosterone.²²

Destructive lesions of the anterior hypophysis from whatever cause obviously may result in changes in testicular function after puberty, just as in experimental hypophysectomy, and are similar in nature to the prepuberal causes of hypophyseal destruction. Aneurysm of the internal carotid artery

invading the sella turcica, adenomas of the hypophysis, and tuberculosis and syphilis involving the gland are usually adult, rather than prepuberal, complications.

Similarly, disorders of the remaining endocrine glands are more apt to occur in the adult and may affect the gonads, although whether directly or indirectly through the anterior pituitary is not clear. Toxic goiter may lessen libido and spermatogenesis,²³ and there may be a fall in urinary neutral 17-ketosteroid excretion.²⁴ Hypothyroidism may affect the testes to a marked degree, also with complete loss of function as a consequence.²⁵ Adrenal disease is also associated with gonadal difficulties.²⁵ This is true in Cushing's syndrome, now generally accepted as a disorder due to excessive adrenal cortical steroid effect,²⁶ though the primary disturbance may be elsewhere than in the adrenal. This disorder is associated with impotence and loss of testis function early in its course. Loss of adrenal cortical function, Addison's disease, usually does not cause striking testicular changes, although it may do so. Sterility may occur and the internal secretory function may fail in the acute stage of Addison's disease, to be restored upon restitution of blood pressure and of the blood sodium level to normal. This is shown by a decline in urinary neutral 17-ketosteroid excretion to zero in the acute phase, and a return to normal with recovery.²⁷

In summary, gonadal failure may occur before or after puberty and may involve tubule or Leydig cell function or, as is usually the case, both. The cause of such disturbances may be genetic, embryologic, physiologic or pathologic in origin. Treatment is dependent on the primary disorder and its amenability to correction.

CLINICAL ENTITIES

Primary Prepuberal Gonadal Failure, or Eunuchoidism. The symptoms and signs of

this disorder are essentially those of failure to initiate or to complete the transition from the infantile to the adult status. Lack of testosterone effect explains all changes except sterility. Muscle weakness, obesity and unusual stature may be noted. Emotional problems may occur and usually result from the patient being aware that he is different from other boys of the same age. There is generally no evidence of spontaneous interest in the opposite sex and sexual activity is dormant.

Little has been added recently to the clinical descriptions of this disorder. The ultimate stature of the patient is unpredictable. One type of eunuchoid is classically stunted, probably due to failure of the puberal growth spurt which normally follows testosterone secretion by the maturing gonad. In these, the epiphyses usually fail to close and growth may occur, upon institution of replacement therapy, as late as at twenty-five years of age. Another type of eunuchoid is taller than normal. There is no adequate explanation for this except that the same phenomenon of overgrowth occurs in young castrates.²⁸ Body fat distribution varies considerably in different cases. Some tend to be unusually thin, others normal, and most tend to be moderately obese with a female body contour due to padding of the hips with fat and to occasional gynecomastia. The absence or markedly limited development of secondary sex characteristics, such as the voice, muscles, the youthful appearance due to lack of hair recession or loss, and the absence of graying, seborrhea, or acne are conspicuous and result from the lack of testosterone effect.²⁹ Later the skin ages prematurely. A slight degree of development of the penis and pubic hair occur frequently though these may be absent. This growth may come from slight testis secretory activity, or possibly from compensatory adrenal androgen output.³⁰ The testes are generally infantile but may

be somewhat larger, though flabby in consistency and insensitive to pressure. The prostate is generally impalpable. Ratios involving sitting height, standing height, length of arms, etc., are of interest to the anthropologist but have largely dropped out of clinical use.

The laboratory findings in this condition are of interest but are generally not pathognomonic. The introduction of the colorimetric method for determination of urinary neutral 17-ketosteroid excretion^{31,22} led to the hope of objective diagnosis of testicular underfunction. However, the steroids of both the testis³³ and the adrenal cortex³⁴ are metabolized and excreted in large part as neutral 17-ketosteroids, roughly two-thirds of the amounts excreted coming from the latter and one-third from the former.¹⁷ Thus a slight increase in adrenal activity may obscure a relatively large decline in testosterone output. Values in eunuchoidism vary from infantile to adult normal levels. (Table I.)³⁵ Since systemic disease and especially disease of the pituitary, adrenal and thyroid glands may produce similar changes in 17-ketosteroid excretion,³⁶ this determination is not of diagnostic value. Testosterone therapy increases the urinary 17-ketosteroid output since the administered hormone is metabolized and excreted in the same way as is the endogenous hormone,³³ whereas methyl testosterone is not so metabolized and may decrease the urinary 17-ketosteroid excretion, probably by anterior pituitary depression. Partition of the total urinary 17-ketosteroids into alpha, beta, alcoholic and non-alcoholic fractions is possible³⁷ but no results have been reported in gonadal failure.

Estrogen seldom appears in the urine in this condition. (Table I.) If present, it is presumably adrenal in origin³⁸ although other sources have been suspected. The urinary output of gonadotropin from the anterior pituitary is generally low. (Table I.)

Occasionally, it is at castration levels. (Table I.) The low outputs have suggested, as mentioned above, that lack of anterior pituitary function may be the cause of testicular failure in some instances of eunuchoidism. However, another explana-

TABLE I
EXCRETION VALUES OF URINARY GONADOTROPIN,
ESTROGEN, AND TOTAL NEUTRAL 17-KETOSTEROIDS
IN A SERIES OF EUNUCHOID PATIENTS

Patient No.	Urinary Gonadotropin M.U./24 Hours	Estrogen R.U./24 Hours	Total neutral 17-ketosteroids Mg./24 hours
333			14.6
255	80	less than 5	11.0
324	80	less than 20	10.8
437	less than 80		9.3
377	less than 60	less than 5	9.3
183	less than 10	less than 5	9.1
132	less than 5	less than 5	8.6
188	40		8.6
23	less than 10	less than 5	8.6
265	30	less than 5	8.6
273	5	less than 5	7.3
520			6.8
217	10	less than 5	4.8
98	120	less than 5	4.8
368	20		4.3
249	less than 5	less than 5	2.6
Normal range	less than 5-40	less than 5-20	7.0-17.0

tion for the low urinary titers of gonadotropin may be that enough testosterone is secreted by the inadequate testes to prevent a castration output by the hypophysis, but not enough to produce secondary sex changes.

The blood count is altered in that the hemoglobin and red blood cell count approach childhood levels.³⁹ Basal metabolic rate determinations are generally in the low normal range. X-rays of the epiphyses usually show delayed fusion, even as late as twenty-five years of age. Creatin is generally present in the urine of the eunuchoid, not having disappeared at the usual age of puberty. There is decreased tolerance to in-



FIG. 1. Fröhlich's syndrome. The original case before operation on the hypophysis. (Reproduced from Fröhlich's original report.)⁴³

gested creatin⁴⁰ as in childhood. Laboratory examination for sperm shows a scanty ejaculate, if any, which contains detritus and a few cells but no viable sperm. Testis biopsy affirms the absence of spermatogenesis and generally shows a change in the morphology of the Leydig cells which is difficult to interpret.^{41a,b}

All the above laboratory changes are corrected by testosterone, except the absence of spermatogenesis and the histologic changes.

Prepuberal Secondary Gonadal Failure due to Destruction of the Hypophysis, or Fröhlich's Syndrome. In 1898, Babinski⁴² described a syndrome of genital underdevelopment and moderate obesity in a girl, secondary to a tumor in the region of the pituitary gland and involving the hypothalamic area. One year later, Fröhlich⁴³ described the same clinical picture in a boy with a carcinoma of the pituitary gland. Since then the obese eunuchoid, and the healthy but obese boy whose sexual maturation has not yet clearly advanced have been confused with the picture described by Fröhlich. A glance at the picture of Fröhlich's original case (Fig. 1), shows the discrepancy between the original case and the subjects now diagnosed as instances of the syndrome. (Figs. 2 and 3.) Obese boys practically always initiate testicular function and mature spontaneously without glandular therapy if left alone⁴⁴ so that avoidance of unnecessary therapy in this group must be emphasized. Certainly, such therapy is not warranted before the end of the normal period for the onset of puberty, i.e., the sixteenth year.

Replacement therapy in Fröhlich's syndrome requires a potent anterior pituitary extract to take the place of the secretions of the destroyed gland. Clinically effective anterior pituitary preparations are not available but pregnant mare's serum hormone⁴⁵ has helped and methyl testosterone⁴⁶ provides very satisfactory relief. The primary intracranial lesion obviously must be treated as indicated.

Postpuberal Primary Non-destructive Gonadal Failure—The Male Climacterium. In about 40 per cent or more of male castrates, young or old, there are vasomotor symptoms similar to those of the female menopause^{28,47}—flushes, sweats, muscle weakness. It is not unreasonable, therefore, that a spontaneous decline in gonadal function in the male has been postulated. It is said to occur at about the same age as in the female and is asso-



FIG. 2. A. F., No. 549845, age twelve years; untreated obesity; to illustrate the difference from true Fröhlich's syndrome with injury to pituitary and hypothalamus. (Fig. 1.)



FIG. 3. A. F., No. 549845, age seventeen years; untreated obesity; to illustrate spontaneous puberal maturation without therapy.⁴⁴

ciated with similar symptoms as the female menopause, plus impotence and loss of libido.⁴⁸ The frequency of diagnosis of this syndrome varies greatly in different clinics. A clear explanation of this discrepancy is not at hand. It is certain, however, that the occurrence of instances of true spontaneous male climacterium decreases as more care is taken to rule out psychogenic and other disturbances.

A study of patients in the older age groups with carcinoma of the prostate indi-

cates an almost universal betterment of the carcinoma after castration.²² Serum acid phosphatase falls if previously increased. Since both growth of the carcinoma and the increased phosphatase level depend on testosterone, it is clear that some degree of testosterone secretion is almost universally present in older men beyond the age of climacterium. Thus it is implied that if the male climacterium is due to gonadal failure, it must be a reduction and not complete cessation of gonadal secretion (such as occurs in the female at the menopause) which has

caused the symptoms. Possible evidence for such a decline in function is found in the decreasing but persistent excretion of neutral urinary 17-ketosteroids with advancing age.^{49,50} Study of the testis histologically after castration for carcinoma of the prostate shows poor correlation with the testicular function indicated by the clinical response to the operation.

Against the hypothesis that simple reduction and not complete disappearance of circulating testosterone is the cause of vasomotor symptoms, is the similar incidence of such symptoms in the old and in the young following castration. This indicates that whatever testosterone is still circulating in older men is still sufficient to prevent symptoms, despite previous decreases in rate of secretion. Were it not for the dangers of testosterone therapy, the point would be academic and suspected cases of climacterium could with impunity be given testosterone as a therapeutic trial. However, the malignancy of carcinoma of the prostate is increased by such treatment and spermatogenesis is arrested. Moreover, when a psychoneurosis and not gonadal failure is the cause of loss of libido and impotence, the psychological disorder tends to become fixed by spectacular and repeated therapeutic efforts and the subsequent chance of psychotherapeutic efforts being effective is lessened. All in all, the author believes that the syndrome of spontaneous male climacterium is not common. Certainly objective confirmation of the diagnosis should be obtained when possible by demonstration of castration levels of hypophyseal gonadotropin in the urine.

Secondary Gonadal Failure in Cirrhosis. Testicular atrophy and cessation of spermatogenesis is a common pathological finding in cirrhosis of the liver. The usual symptoms of testicular failure, however, i.e., loss of libido, impotence, sterility and muscular weakness are often lost sight of due to the

predominance of more serious symptoms. The scanty secondary sex-hair of these people may conceivably be due to testicular failure but is more probably due to a constitutional factor. The mechanism for this disturbance may be two-fold: First, gonadotropin output of the anterior pituitary is sharply restricted in malnutrition¹⁹ and in thiamin deficiency.⁵¹ Second, inactivation of free circulating estrogen by the cirrhotic liver is interfered with²¹ both because of actual loss of liver parenchyma and because of the absence of thiamin, which appears to be necessary for the liver cells to perform this function optimally.⁵² Thus, estrogen arising from the adrenal in the male may accumulate in the blood, depress the anterior pituitary, and so result in testicular atrophy. Testosterone inactivation by the liver does not appear to be affected in thiamin deficiency although obviously, serious liver parenchyma destruction will lessen the ability of the organ to inactivate this hormone also.

Secondary Gonadal Failure in Other Systemic Diseases. Although the signs and symptoms of testicular failure may occur in many systemic diseases, just as in cirrhosis, the symptoms of the major disease generally obscure those arising from testicular failure. Correction of the underlying disease results in restoration of testicular function. Thus proper diagnosis and not gonadal replacement therapy is indicated in most instances. In the laboratory, gonadotropic and urinary neutral 17-ketosteroid excretion are moderately depressed, generally not absent.⁵³

Sterility. Testicular failure, from whatever cause, usually involves both the spermatogenic and internal secretory functions, with resultant sterility. Proper diagnosis and correction of the original disorder, when possible, usually results in spontaneous return of sperm production to normal. Alcoholism is listed as a systemic cause of cessation of spermatogenesis but the asso-

ciated malnutrition and vitamin deficiency probably account for the effect on the testis rather than a direct toxic effect of the drug.

A group of cases with testes of normal size and with normal secondary sex characteristics, but almost no sperm production, deserves mention.⁵⁴ There is no demonstrable cause for the failure of spermatogenesis nor is hormonal treatment effective. One possible explanation for the aspermia of this group may be some genetic fault in tubule cell differentiation and function.

Impotence and Premature Ejaculation. These disorders are almost always psychogenic rather than gonadal in origin when definite organic change is not evident. The only objective criteria for a testicular origin of these symptoms would be the demonstration of aspermia and of castrate amounts of pituitary gonadotropin in the urine. Even then, after true castration, the effect of the psyche is large since not all patients lose their potency⁵⁵ and premature ejaculation is quite uncommon if libido is preserved.

TREATMENT

The goal of treatment in testicular as in other disorders is to establish an etiologic diagnosis and to correct the basic disturbance when possible. In most instances, gonadal failure in man is secondary to a systemic disorder which is correctible, such as toxic goiter, malnutrition, cirrhosis, etc., and no specific treatment for the testicular failure is indicated. In primary gonadal failure, or eunuchoidism, on the other hand, the sole problem is treatment of the testicular failure and the aim of therapy is to stimulate the testes. This is not always possible, so that replacement therapy is often necessary. This latter corrects the symptoms and signs of testosterone lack but does not affect the aspermia.

As stated above, recent work suggests that more, rather than fewer, cases of eunuchoidism are due to lack of anterior hypophyseal

gonadotropin secretion. A program of therapy to stimulate the testis has been devised⁶⁴ using chorionic gonadotropin from human pregnancy urine and a specially prepared, not yet generally available, pituitary follicle-stimulating substance. This has produced spermatogenesis histologically, as shown by testis biopsy and has caused development of secondary sex characters in these patients.^{16,55,56} However, sperm examinations and fertility results following such therapy are not yet reported. The chorionic gonadotropin has a luteinizing or interstitial cell stimulating effect, while the anterior pituitary extract is follicle or tubule stimulating. No so-called antihormone response^{57,58} results from treatment with human-derived hormone since the material is not a foreign protein and so does not cause the production of an antibody. However, animal-derived anterior pituitary extracts are antigenic and so are useful for short periods only.⁵⁹

Gonadotropin therapy, to be successful, must be given by injection daily, or three times weekly. A dosage of 1,500 I.U. of chorionic gonadotropin together with an experimentally determined amount of follicle-stimulating material, depending on the preparation, is given for some weeks. Pregnant mare serum hormone has been used for short periods, instead of the hypophyseal follicle stimulator.¹⁶

When the testes are missing, or when the above program is inadvisable or has failed, replacement therapy with testosterone is employed and, except for lack of sperm production or increase in testis to normal size, is completely successful. This therapy, as with insulin in diabetes, must be continued and adequate dosage must be given. Suboptimal dosage may produce little or no visible changes and thus lead to the discontinuance of a therapy which is always successful when sufficient hormone is administered. The illustrations from a series



FIG. 4. A. P., No. 562365, age sixteen years; aplasia testis, untreated.

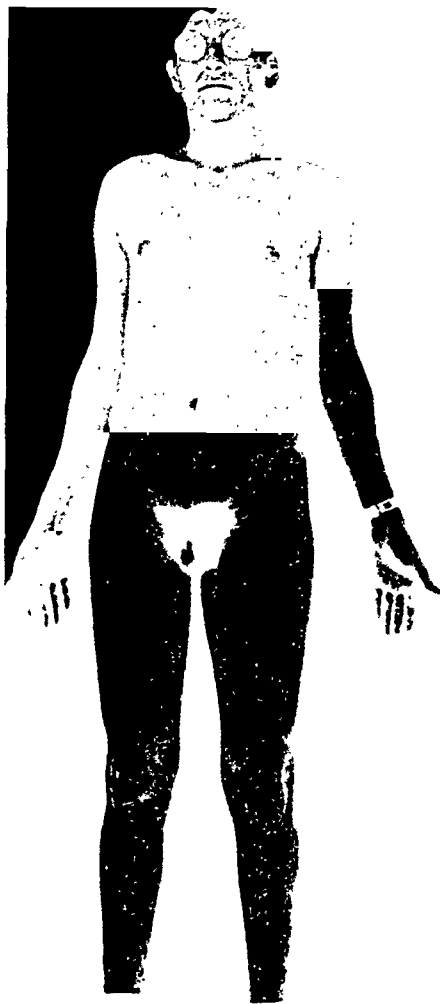


FIG. 5. A. P., No. 562365, age twenty-one years; aplasia testis after male hormone therapy for five years.

of patients treated for three to six years in the Presbyterian Hospital and Thyroid Clinic of the Vanderbilt Clinic (Figs. 4 to 7) indicate the results obtainable with adequate therapy.

Methyl testosterone, as androgen therapy, is used exclusively in most clinics because it can be given by mouth. As stated, the substitution treatment of eunuchoidism is chronic. Continued injections of testosterone propionate in oil, 0.025 Gm. three times weekly, and repeated implantations of pellets, absorption from which is uncertain, are inconvenient and do not seem justifiable except temporarily. Free testosterone and,

testosterone propionate are largely inactivated by mouth, unlike the methyl derivative, and so the oral route is not available. Sublingual administration is used but is uncertain and is inefficient if the material is not retained long enough before swallowing. Methyl testosterone meets these objections. It is effective by mouth and its effects are identical in every way with those of testosterone except for the production of an intense creatinuria^{60,61} in the usual dosage of 0.03 to 0.06 Gm. per day. No toxic symptoms have been reported.

Recently, however, the suspicion that

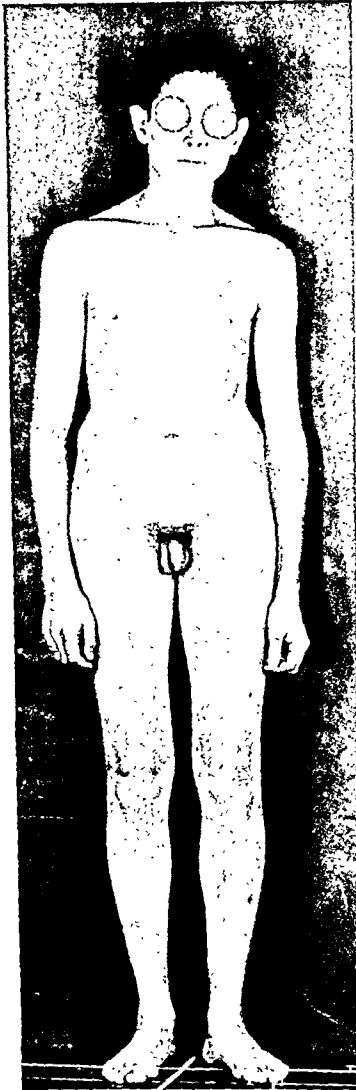


FIG. 6. A. L., No. 567231, age twenty-five years; eunuchoidism, untreated.



FIG. 7. A. L., No. 567231, age thirty years; eunuchoidism, after male hormone therapy for five years.

jaundice may be produced by methyl testosterone has been raised in three cases in the author's series.* The clinical picture was the same in all three cases, that of hepatitis with a peculiar protracted course and with a low blood alkaline phosphatase and a repeatedly negative cephalin flocculation test. There is an early obstructive phase with bile in the urine but not in the stools. Six other cases of jaundice associated with methyl testosterone have been cited to the

* In a fourth case seen recently, jaundice did not recur with a retreat of the drug.

author* but in only one case† was the drug given a second time, upon which there was a recurrence of jaundice. The other five instances might have been instances of intercurrent infectious hepatitis.

The results of adequate testosterone administration are striking, and the transformation from the infantile state to adulthood is similar in every respect to that during

* Cases of Drs. Reid R. Heffner, New Rochelle, N. Y., Joseph Eidelsberg, New York, N. Y. and E. Perry McCullagh, Cleveland, O.

† Case of Dr. Reid R. Heffner.

normal puberal maturation. Muscle development is promoted, there is gain in weight and often an increase in height. In one case (Fig. 5) there was a gain of 76 pounds and 11 inches in five years. Secondary sex hair appears during therapy but its amount and distribution are influenced by hereditary and constitutional factors. Penis, prostate and seminal vesicle growth, and evidences of sexual activity are all promoted to the appropriate chronological level. Marriage is undertaken and consummated in most cases.

Acne appears early and may be severe and annoying. A slightly reduced dosage helps this condition, although most patients resist any attempt to lower dosage. Once treatment is started, complete cessation of the hormone therapy may result in marked muscular weakness, leg pains, loss of libido and erections and an anxiety state. These are instantly corrected by renewal of the drug.

In the castrate and male climacterium patients, successful replacement therapy is possible with methyl testosterone 0.03 and 0.06 Gm. a day just as in the eunuchoid group. A combination of methyl testosterone and estrogen, e.g., stilbestrol, has possibly been more effective than androgen alone in restoring strength and alleviating vasomotor symptoms.

Testosterone therapy is often given to men with adequate testicular function but with psychogenic loss of libido or impotence, or with *misdiagnosed male climacterium*. Repression of spermatogenesis, activation of carcinoma of the prostate as shown by increase in the acid phosphatase in the blood, or the exaggeration or fixation of neurotic trends are possible consequences of such therapy, which cannot be considered lightly.

The emotional problems of patients with testicular failure are important.^{62,63} The borderline eunuchoid may be suffering from

psychogenic impotence in addition to his physical difficulty. The loss of libido is then not entirely correctible by adequate replacement therapy. Here the hormonal drive is adequate but the emotional block prevents adequate activity or direction to the stimulus, the same mechanism that disturbs the physically normal male with psychogenic impotence. Obviously, psychiatric help from trained sources is indicated.

In summary, poor response to replacement therapy with male sex hormone generally suggests that the diagnosis must include sites of disorder other than the testes proper. It should be emphasized that unless there is certain evidence that gonadal failure exists as a result of primary testicular or pituitary failure, testosterone or gonadotropin therapy is unnecessary, possibly harmful and probably futile. Cure of a primary disease originating outside the testis, if such a disease is present, is all that is necessary to treat the secondary gonadal difficulties.

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Seminar on Thromboembolism

Mechanism of Blood Coagulation*

JOHN H. FERGUSON, M.D.

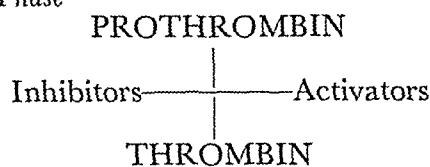
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BLOOD coagulation is essentially a series of colloidal chemical reactions¹³ normally proceeding only after blood is shed, but also occurring pathologically¹⁵ within the vascular system as a factor in thromboembolism and in blood or plasma extravasations (fibrinous exudates).

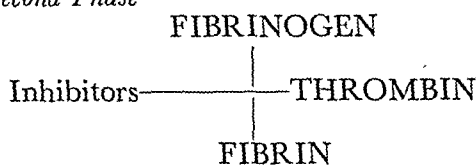
Nature of Clotting Mechanism. The logical approach to an understanding of the mechanism of coagulation along strictly biochemical lines is rendered difficult by the complexity of agents involved.¹⁴ Water, pH, salts (e.g., Ca ions), proteins (e.g., fibrinogen and fibrin, prothrombin and thrombin), fatty substances (e.g., the phospholipids and cephalin), carbohydrate derivatives (e.g., heparins) and a complex system of proteolytic enzymes are all clearly implicated and their modes of interaction extend into the farthest reaches of chemistry, including some highly specialized divisions of physical, colloidal and enzyme chemistry. Nevertheless, as a result of carefully controlled *in vitro* experimentation, the basic mechanisms of clotting are now fairly well understood and can be presented in a straightforward manner if the logic of the methods of study is comprehended.

The clotting processes, which are largely simultaneous in ordinary coagulation of the blood, are primarily plasma phenomena that can be separated experimentally into two phases:

First Phase



Second Phase



Fibrin is the essential material of the clot. It is deposited as a semisolid quasicrystalline "gel" when the colloidal solution of its plasma protein precursor, fibrinogen, is acted upon by a specific coagulant, normally thrombin. It is only necessary to inject a potent thrombin solution intravenously into an experimental animal and to observe the prompt intravascular coagulation (thrombosis) to confirm the rather obvious fact that active thrombin is not normally present in the circulating blood. What the plasma does contain is a protein precursor, prothrombin, which can be isolated and made to yield thrombin by appropriate activation procedures.³² Ordinarily, these coagulation reactions are subject to a variety of inhibitory mechanisms, many of which can be elucidated *in vitro*.²⁹

Nature of Fibrin Formation. The typical (quasicrystalline) microscopic "needles" or "filaments" of fibrin, best seen under dark-field, are shown in Figure 1. The cited

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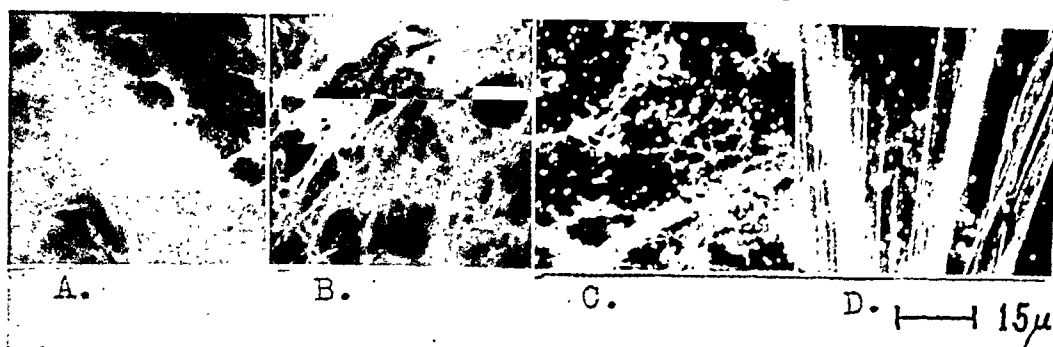


FIG. 1. Dark field microscopy (oil immersion lens) of fibrinogen (dog) mixed with A, tryptase-free thrombin; B, crystalline papain; C and D, ninhydrin. (FERGUSON, J. H. and RALPH, P. H. *Am. J. Physiol.*, 138: 648, 1943.)

experimental data¹¹ demonstrate a thrombin-like action of crystalline papain (which, unlike thrombin, is a proteolytic enzyme) but differentiate true fibrin from the non-descript fibrinogen denaturation produced by ninhydrin and a wide variety of other chemical agents. The exact chemistry of the thrombin-fibrinogen interaction is not yet understood. It is known that fibrinogen molecules, despite a high molecular weight (about 500,000),⁵ are extremely attenuated or filamentous, so that in a moving fluid they tend to orient themselves "like logs in a stream." If the logs can be made to pile up in a criss-cross manner they tend to form a mass which blocks the stream. This rather crude analogy can be presented in a technical nomenclature ("coacervation")²⁶ as a basis for a fundamental explanation of fibrin gel formation and its rôle in thromboembolism. The underlying forces and particularly the part played by thrombin have still to be worked out. Facts,¹⁵ relevant to the suggestion that electrochemical forces participate, include the difference between isoelectric points (pH) viz., fibrinogen 5.4, thrombin 4.4. The very minute amounts of thrombin needed and certain other data are compatible with the view that thrombin is a special type of enzyme.

*Experimental Study of Clotting Reactions in vitro.*¹⁰ Despite considerable progress⁵ in recent years, few of the chemical agents concerned in the clotting process can be

isolated and determined with quantitative precision. Ordinary analytical methods especially fail to detect traces of impurities which may markedly modify behavior in clotting tests. For such reasons, it is desirable to comment briefly upon a technic for circumventing these difficulties during the study of the basic clotting reactions *in vitro*.¹⁵

*Conditions Affecting Coagulation.*³¹ The colloidal reactions are influenced by (1) temperature, (2) pH, (3) salt concentrations, (4) concentration (dilution) of specific factors, (5) adsorption and other colloidal phenomena. In the last category are the well known effects of "wetable" surfaces (e.g., blood clots more easily in glass than in paraffined, plastic or silicone-treated tubes) and the clot-aiding or "fibrinoplastic" (second phase) effect of gum acacia and a variety of non-specific adsorptive colloids. The first step, therefore, is to standardize these experimental conditions.

Purity of Reagents. Secondly, while it is desirable to employ isolated reagents as pure as possible, it is even more important to test each reagent and combination of reagents to rule out any significant effects of impurities which can modify the clotting tests.

Timing Reactions. Finally, the reactions are carefully timed with reference to a specific end point, especially clotting time (c.t.). By confining the experimental analy-

ses to similarly constituted mixtures of the same batch of reagents, uncontrollable variables are minimized and the data obtained assume a quantitative as well as qualitative significance. The examples of Figures 2 and 3 illustrate the above points.

the above stated basic fact that a shorter clotting time (under standardized conditions) means more thrombin; this fact may be applied in numerous practical ways.

Prothrombin Activation Curves (Fig. 3). When a prothrombin solution, mixed with

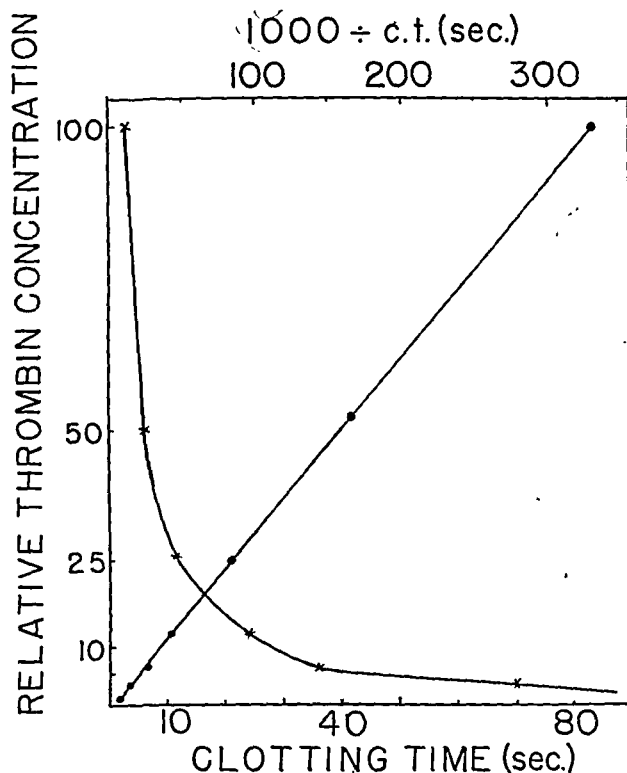


FIG. 2. Clotting time and relative thrombin concentration (percentage). The inverse law: Clotting times (sec.) and $1000 \div \text{c.t. (sec.)}$ of 1.0 cc. fibrinogen (bovine, 1:200) + 0.25 cc. thrombin (bovine, 1:500); borate buffer (pH = 7.7); temp. = 25°C.

Clotting Time and Relative Thrombin Concentration (Fig. 2). When a series of thrombin dilutions is tested on a given fibrinogen solution, it is easy to observe that the stronger the thrombin the shorter is the clotting time. The strength of the fibrinogen is of very minor importance between 1.0 and 0.2 per cent. Under somewhat limited experimental conditions, the c.t. is inversely proportional to the thrombin concentration and the latter may be expressed as percentages or units in terms of an empirical dilution technic. It is quite unnecessary to go into technical details in order to grasp

suitable activators (v. below) is sampled at successive time (incubation) periods and the clotting time of each measured sample added to a test fibrinogen is noted, the graphic plot of the data obtained yields what we call "the prothrombin activation curve." Again the technicalities with reference to rate and amount of thrombin formation are subsidiary to the simple indication of increasing amounts of thrombin as detected by the shorter clotting times. When the curve levels off at the shortest c.t. the activation under the prevailing conditions is 100 per cent complete.

The factual statements in the following paragraphs are supported by experimental modifications of the simple methods we have just outlined.

ACTIVATORS OF PROTHROMBINS²

The factors which participate in the conversion of prothrombin to thrombin may be considered each in turn.

complete thrombin formation. Oxalates or citrates, etc., depress the ionization of calcium. Added early enough (Zone I of Figure 3) they can completely prevent the activation of thrombin. Added too late, the thrombin being fully formed (Zone III of Figure 3), they are unable to prevent clotting and have only a very minor non-specific

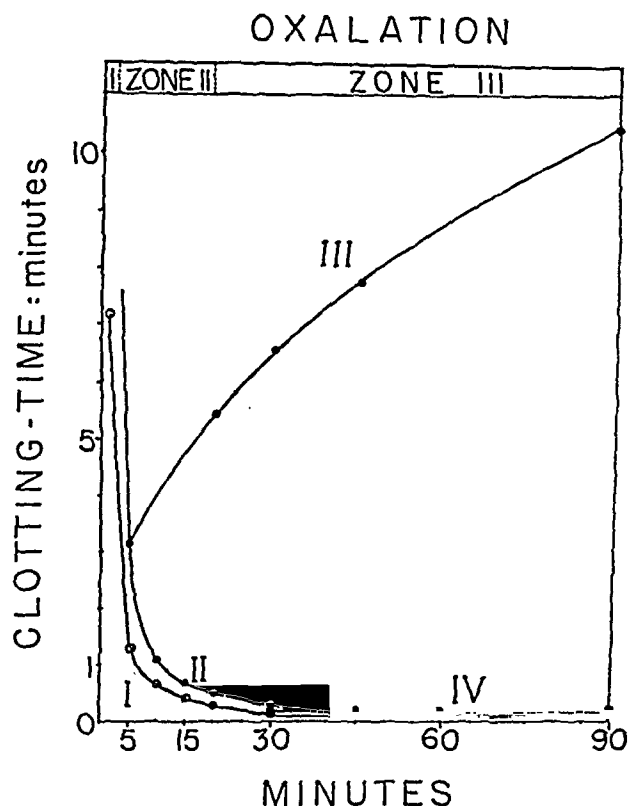


FIG. 3. Prothrombin activation curves and effects of oxalation. II, \bigcirc — \bigcirc prothrombin (bovine, 1:200) + brain thromboplastin + M/10 CaCl_2 ; clotting times of 0.25 cc. sample + 0.25 buffer + 1 cc. fibrinogen (25°C.); II, \bullet — \bullet same mixture tested on oxalated fibrinogen; III, \bullet — \bullet same mixture oxalated after five minutes and tested at intervals on fibrinogen. (Volumes of thrombic mixture and oxalate in clotting test same as in II); IV, \times — \times same mixture oxalated after thirty minutes and tested as was indicated in step III.

Calcium.⁸ Calcium ions (Ca^{++}) are ordinarily essential for the first phase of the clotting mechanism. They are not needed for the second phase (thrombin-fibrinogen interaction) and an excess is inhibitory owing to certain non-specific salt effects. Too little calcium results in slow and in-

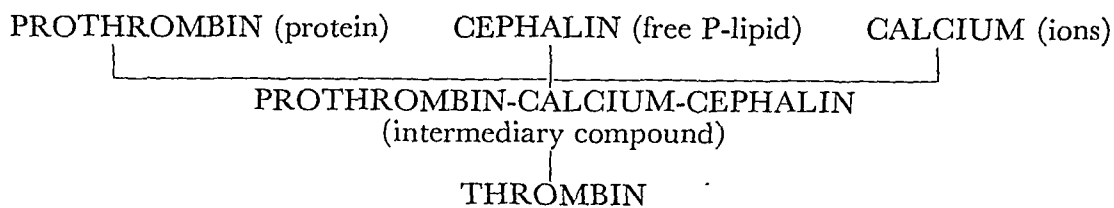
clot retarding effect in excessive concentrations. There is, however, an intermediate zone (II) during which a large excess of oxalates (or citrates) can progressively inactivate the thrombic mixture. Re-addition of calcium restores the activation. This we explain as evidence for the existence of a

calcium-containing *intermediary complex* (with prothrombin and phospholipid) existing briefly during thrombin formation (v. infra). The final thrombin may be obtained free of calcium by oxalation and electrodialysis.

In the normal plasma or serum there is about 10 mg. per cent. of calcium. More than half of this is ionized and the rest is in protein-bound and other non-available forms. When blood is oxalated or citrated and subsequently recalcified there are a series of equilibrations between ionized and bound forms of calcium and the time factors involved are nearly as important as the amounts. The following statements are supported by experimental evidence and have direct clinical significance: (1) the normal blood Ca^{++} level is about optimal for coagulation; (2) the minimum Ca^{++} requirement for clotting is well below any level encountered in the severest hypocalcemia (e.g., tetany); (3) clinical hypercalcemia and attempts to raise the blood calcium therapeutically do not significantly modify the clotting process. The only possible clinical application of the *in vitro* data on calcium and coagulation is suggested by recent reports²¹ that calcium is a variable in the prothrombin clotting time (p.c.t.) test (v. infra) especially in the hypopro-

and poorly. There is evidently need for an additional factor or factors for which the descriptive term "thromboplastic" is widely used.¹⁴

Phospholipid. Cephalin (phosphatidylethanolamine) is a phospholipid substance which can be isolated by chemical means from plasma, cells and tissues (especially the brain). It has no direct action on fibrinogen or on prothrombin alone, but in the presence of Ca^{++} , it is a thromboplastic agent demonstrably active even in dilutions of 1:1,000,000. Inadequate amounts, however, result in slow and incomplete thrombin formation. Optimal amounts complete the conversion of prothrombin to thrombin in a very few minutes. The final thrombin may be obtained free from phospholipid. There are still technical difficulties in obtaining phosphatide-free prothrombin, however, so that we can at present merely point to experimental evidence that cephalin usually participates in thrombin formation only when available in the "free" state, as compared with protein-bound forms in which the cephalin is not available. Like calcium, therefore, the phospholipid appears to act via an intermediary complex or compound. These views are summarized as follows:



thrombinemia due to dicumarol which is one of the modern methods of treating and preventing thromboembolic conditions. We except, of course, the important use of citrates for blood transfusions, etc.

Thromboplastic Factors. It is possible, though with difficulty, to prepare prothrombin solutions which are not activated by calcium salts alone, or only very slowly

Although data are negative for other currently recognized phospholipids, there are a few suggestions pointing perhaps to as yet unidentified thromboplastic agents of this class.

Thromboplastin (Thrombokinese). The long observed fact that the fat-soluble phosphatides are not as potent as the similarly acting crude, watery tissue extracts justifies

the continued use of names like thromboplastin or thrombokinase for the latter. A macromolecular protein complex containing phosphatides³ has recently been isolated from lung extracts and is said to be an extremely potent thromboplastic agent. It is also said to lack demonstrable proteolytic properties such as are frequently encountered in crude aqueous tissue extracts, including most commercial thromboplastins.

In general, thromboplastins require Ca^{++} but differ from cephalin in three important respects, namely, (1) greater potency, (2) effectiveness in presence of heparin (v. infra) and (3) greater ability to restore clotting time to normal when added to hemophilic plasma. The defect in hemophilia is certainly related to the thromboplastic system.²⁹

Tryptase (Plasmin or Fibrinolytic Enzyme). The additional thromboplastic actions of thrombokinase can be imitated *in vitro* by simply adding a small quantity of crystalline trypsin (pancreatic enzyme)⁷ to the ordinary $\text{Ca} + \text{cephalin}$ activator system. Trypsin also resembles thromboplastin in the dangers of intravascular coagulation and shock-like phenomena which follow intravenous injection and preclude any such use *in vivo*. With great care, perhaps aided by the protective action of natural trypsin-inhibitors in the blood, one or two hemophilic patients³⁴ were recently found to tolerate enough trypsin intravenously slightly to lower their clotting time for a brief period. These data are of no clinical significance but support the idea that a proteolytic enzyme resembling trypsin may play a rôle in blood clotting. We have experimental data to suggest that trypsin is not a thromboplastic agent in its own right but merely a factor which catalyzes the actions of cephalin and calcium when thrombin is being formed in the presence of interfering proteins. Obviously, this could be of great importance in the natural clotting system because of the

occurrence of trypsin-like enzymes in the blood.¹²

These enzymes have been recognized since the turn of the century and are often called fibrinolysin or fibrinolytic enzyme, when studied in connection with fibrinolysis or digestion of fibrin, a phenomenon which occurs to a variable degree in natural blood clots.²⁷ The term tryptase¹² merely means trypsin-like (as opposed to the cathepsins and possibly other types of blood proteases) referring especially to alkaline pH optimum (7.5 ± 0.5), ability to attack a variety of ordinary protein substrates (casein, gelatine, hemoglobin, fibrin, fibrinogen, etc.) and susceptibility to ordinary trypsin-inhibitors. It differs from pancreatic trypsin, however, in (1) origin, (2) specific activator (kinase)²² and (3) other important ways.⁴ For these reasons, the new name, *plasmin* has been suggested⁴ but perhaps somewhat prematurely. Our strongest reason for preferring tryptase is to emphasize the numerous analogies to the pancreatic enzyme. For instance, the plasma enzyme resembles its prototype²⁸ in (1) inactive precursor (tryptogen), (2) need for a specific activator (tryptokinase, e.g., streptokinase, miscalled, "streptococcal fibrinolysin"²²), staphylokinase and similar activators of bacterial origin), (3) inhibition of active enzyme (anti-tryptase) and of the kinase (anti-tryptokinase, miscalled "antifibrinolysin").²² Antitrypsins (crystalline) from pancreas^{9,18} and soybean^{25,35} have certain anticoagulant effects.

Some very recently published experiments¹⁷ afford clear proof of the trypsin-like thromboplastic action of natural tryptase from a variety of plasma protein preparations. For both enzymes it must be emphasized, this clot aiding effect requires much smaller amounts of enzymes than are needed for ordinary proteolytic effects, including fibrinolysis, fibrinogenolysis (which we use for an enzyme assay method sensitive

to 1:1,000,000 of standard trypsin), prothrombinolysis, etc. These proteolytic phenomena are essentially independent of the clotting mechanism but do encroach upon the coagulation problem at several points, e.g., (1) in the preparation of the protein clotting factors (the protease impurity is very difficult to get rid of); (2) clot-retraction and fibrinolysis (since pure thrombin-fibrin is a stable gel for weeks at 37°C., clot-retraction and fibrinolysis obviously require an additional factor and this is readily supplied by the addition of trypsin or tryptase-containing materials, including platelets); (3) fibrin resolution in the body, e.g., liquefaction and removal of thrombi and other fibrin clots, resolution of fibrinous exudates, liberation of emboli from thrombi formed in the circulatory system, etc.; (4) non-coagulability of cadaver- and menstrual-blood because of proteolysis of clotting proteins.¹²

*Clot Inhibitors.*³⁰ Normal serum has a considerable capacity for neutralizing active thrombin both *in vitro* and *in vivo*. The time-honored use of the term antithrombin has never justified itself by an adequate identification of the factor or factors involved.¹⁴ Only one natural agent of clinical importance in this regard has yielded to biochemical attack but it is still imperfectly understood.

*Heparin(s).*¹ The singular is used for convenience but really represents a class of substances having the general composition of mucoitin polysulfuric esters (i.e., complex carbohydrate derivatives) the molecular building stones of which are (1) glucosamine, (2) glycuronic acid, (3) acetic acid (? var.) and (4) ester-linked sulfuric acids. Heparin is believed to originate in the metachromatic-staining, water-soluble granules of the tissue basophils or Ehrlich "mast" cells and to enter the blood stream, particularly in the liver, in small amounts normally

but in considerable quantities in certain conditions, e.g., anaphylactic shock.

Heparin inhibits clotting both *in vitro* and *in vivo*. It acts on the two phases of the clotting system in a manner too complicated to admit of simple description but the most important point is the need for some "co-factor" (heparin-complement or proantithrombin) the nature of which is obscure. This is best supplied by the crude "albumin" fraction of plasma or serum.³⁰ Heparin plus a co-factor is able to prevent the clotting of fibrinogen by thrombin (when either factor alone has very little effect). Even smaller amounts of heparin plus a co-factor suffice to prevent the formation of thrombin from prothrombin. This action may be termed antiprothrombic but the best data suggest that it is chiefly directed against the thromboplastic mechanism (i.e., "antithromboplastic"). The actions of heparin can be neutralized *in vitro* and *in vivo* by the basic protamine, salmine.

*Platelets and Blood Clotting.*³⁶ Heparin also lessens the agglutination and breakdown of the blood platelets but so do most agents which arrest the coagulation process. The significance of this correlation is not yet clear but raises possibilities that some factor may be common both to coagulation and to platelet lysis. Could it be tryptase enzyme? Platelet preparations are thromboplastic, like most cellular and tissue extracts.

This and a variety of other observations have led many observers to give the platelets a part in the normal clotting mechanism which it is very doubtful that they deserve. Since platelet-free plasma undoubtedly clots readily on simple recalcification and is, potentially at least, the source of all the known clotting factors, and because the relative quantity of platelets and any agent (e.g., thromboplastin) they contain is so small relative to the plasma in which they are suspended, it is difficult to see how platelets can make any significant contribu-

tion to ordinary clotting. The clotting time is normal in thrombocytopenic purpura.²⁰ The rôle of agents of (damaged) tissue origin must also be regarded as accessory to the normal plasma clotting mechanism.

Initiation of Clotting in Shed Blood and Intravascularly. When the question is raised as to what we really know of the reasons for the normal fluidity of the circulating blood and for the occurrence of clotting when blood is shed or intravascularly (e.g., in thromboembolism), even the recent advances in our knowledge of the underlying mechanisms are inadequate without a little guesswork in the explanation. That this is risky is borne out by the failure of the theories of the late Professor W. H. Howell,²⁰ long the classical teaching in the United States. The chief failures of the Howell theory are (1) the inadequate development of the inhibitory idea, e.g., Howell's concept of some inhibitor + active agent (antithrombin-prothrombin) combination released from the inhibition by thromboplastin, with the prothrombin then yielding thrombin through the agency of Ca^{++} alone, is not in accord with modern experimental facts; (2) inability to explain the initiation of thromboplastic action except by bringing in platelet and tissue-factors which the experimental evidence and the above mentioned considerations show to be unnecessary.

We are still in the position of having to explain the normal absence of intravascular clotting in terms of lack of active thrombin due, in turn, to non-operation of potential thromboplastic mechanisms. The modern work does, however, clearly prove the direct participation of thromboplastic factors in prothrombin formation (Ca alone is not enough). The basic explanation of clotting must be that the inactive precursor prothrombin (existing as such) requires thromboplastic activation and the non-availability of the latter is the crucial point. Two possible non-availabilities are suggested by

our modern work; first, the non-availability of cephalin in ordinary protein combination. We suggest that the tryptase enzyme is important in mobilizing the phospholipid. The second is the non-availability of tryptase as long as it is in precursor (tryptogen) form and in the presence of antitryptase inhibitors. Our guess¹² is that the ordinary colloidal disturbances ("wetting," adsorption, etc.) when the blood is shed or when it contacts damaged vessel walls or tissues could cause activation of tryptase. This in turn mobilizes the phospholipid and the whole process of prothrombin activation until there is enough thrombin to clot the fibrinogen, either locally (e.g., in mural thrombus formation) or throughout the volume of blood or plasma. The cellular, especially platelet, factors in thrombus formation are probably an important accessory mechanism in thromboembolism since their agglutination and adhesion to damaged endothelium precedes true clotting and could add appreciable thromboplastic factors at the focus where the clot is initiated. There is obvious need for additional experimental knowledge before these views can be regarded as more than a working hypothesis.

The inhibitory mechanisms must be important in the control of each stage of the above series of reactions, viz. (1) inhibitors of the formation and of the action of the tryptase enzyme,²² (2) inhibitors of the thromboplastic mechanism, preventing thrombin formation and (3) inhibitors of active thrombin. These may be regarded as successive lines of physiological defense against the untoward occurrence of coagulation of the blood *in vivo*. Experimental data seem to permit the generalization that these inhibitions are more significant as mechanisms for delay than for completely arresting the phenomena in question. Quantitative interrelationships are important.

PHYSIOLOGICAL CONSIDERATION OF BLOOD CLOTTING

The fundamental mechanism of blood clotting yields to approach from the biochemical point of view. The physiological approach to the subject unites with clinical applications in pointing out the way in which the body can control the various factors involved in both health and disease.²⁹ Fibrinogen¹⁹ and prothrombin² are plasma proteins comprising, according to latest estimates, 0.28 Gm.⁵ and 20 mg.,³² respectively, per 100 cc. plasma. The liver is of special significance in the metabolism of the plasma proteins and there are numerous experimental and clinical data to show that severe liver dysfunction or damage results in lowering of the plasma levels of these proteins with a concomitant bleeding tendency associated with failure of the clotting mechanism. Fibrinogenopenias are rarely significant but hypoprothrombinemias are quite the most common coagulation defect encountered clinically. Considerable practical value attaches, therefore, to the prothrombin clotting time (p.c.t.) tests,³⁷ of which the whole blood ("bedside") method and Quick's plasma prothrombin test are preferred clinically, while the Iowa two-stage method is said to have additional advantages in the securing of research data. None of these tests can meet certain theoretical objections which aim at deciding whether prothrombin, as such, is the only significant variable they measure. When we know more about the thromboplastic and inhibitory factors it is not unlikely that the evaluation of the p.c.t. test will have to be modified. Despite these objections, the prothrombin clotting times are valuable clinically both in diagnosis and treatment. As an example of the latter, we have the use of the hypoprothrombinemic dicumarols²⁴ in the prevention and symptomatic cure of thromboembolism. In order to produce prothrombin the liver must be supplied

with adequate amounts of certain naphthoquinones (vitamins K).⁶ Usually these are readily absorbed from the alimentary canal from bacterial as well as food sources, but deficiency may occur, as in hemorrhagic disease of the newborn and some forms of intestinal disease. Vitamin K therapy requires consideration of absorption (e.g., bile salts and fat-soluble menadione, etc., given orally) and of ability of liver utilization even when water-soluble vitamin K is given parenterally. Large doses of vitamin K supplement transfusions in combatting overdosage of dicumarol during anticoagulant therapy.

The physiological controls of phospholipid and thromboplastic enzyme are unexplored. It is known that cephalin is never deficient and that there are variations in plasma or serum enzyme, at least in active tryptase. The inhibitor problem is also unsolved except for data showing antithrombin and heparin increase in peptone and other anaphylactoid shock.

We can modify the coagulability of the blood *in vivo*, particularly in the direction of prolonged clotting times, both by heparin injections and by dicumarol therapy.³⁰ The former is promptly initiated but hard to maintain, for reasons involving the excretion, destruction (e.g., by heparinase) and other fates of heparin in the body.¹ These topics will be discussed fully in subsequent papers but a preliminary word on the basic mechanisms of action of hypoprothrombinemic agents may be appropriate. Dicumarol or 3,3-methylene-bis (4-hydroxy) coumarin was isolated and identified by Link et al.,²⁴ as the toxic agent responsible for the hemorrhagic disease developed in cattle from eating spoiled sweet clover hay. Quick³⁰ had shown this disease to be characterized by a severe hypoprothrombinemia. Dicumarol, in common with a number of related drugs, has no significant action on the clotting mechanism proper but merely

serves to depress the liver production of the essential factor, prothrombin. In addition to the hypoprothrombinemia there may also be a lowering of the plasma fibrinogen with excessive doses of the drug. In some ways the liver response to these drugs is just the opposite of that to the vitamins K. It is perhaps interesting, therefore, that phthiocol (a vitamin K naphthoquinone from the tubercle bacillus) can be converted into 3, 3-methylene-bis (2-hydroxyl-1, 4-naphthoquinone) which has hypoprothrombinemic properties, and conversely that 3-methyl-4-hydroxycoumarin has some vitamin K activity. Indandione derivatives, chemically related to phthalic acid which antagonizes dicumarol, have the actions not of vitamin K but of the antiprothrombinemic agents. Excess of vitamin K appears to have a liver-stimulating action able to produce hyperprothrombinemia in the normal body as well as to aid in counteracting overdosage by dicumarol. Dicumarol can be synthesized from salicylic acid, and salicylates (especially acetylsalicylic acid) have a weak but quite definite hypoprothrombinemic tendency. A conservative interpretation of all these data emphasizes their close connection with liver cell function and leads to hesitation about postulating any direct chemical antagonisms between the two main types of agents that raise or lower plasma prothrombin, respectively.¹⁵

It is not yet practical to enhance the general coagulability of the blood by any safe systemic procedures other than fresh blood transfusions and, perhaps, the use of certain plasma globulin fractions in hemophilia.²³ Thrombin, especially aided by fibrinogen solution, fibrin foam, fibrin film, gelfoam and soluble cotton (oxidized cellulose) has a wide variety of modern uses as a local hemostatic and coagulant. Thromboplastic preparations are also restricted to

topical use and are in general less effective than the new thrombin materials for this purpose.¹⁴

Finally, in relation to the specific problem of thromboembolism we must consider the rôle of local conditions, especially damage to endothelium of the vessel wall and stagnation of blood flow, freezing (frost-bite), heating (burns), etc. There is room for new detailed information on the exact way in which these factors contribute to the local disturbance in the clotting mechanism. It would seem reasonable, however, to orient the direction of these inquiries along the lines opened up by consideration of the individual factors in the clotting mechanism, as brought out in the experimental analysis and to which we have devoted major attention in the preparation of this review.

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Combined Staff Clinics

Hemolytic Mechanisms

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FRANKLIN M. HANGER: The purpose of today's discussion is to point out some of the factors involved in the breakdown of red blood cells.

It would be quite impossible in the time allotted to enumerate the various hemolytic processes or to present the clinical pictures of the diseases characterized by excessive blood destruction. It is rather humbling to medical science to recognize that despite intensive study by the most refined physico-chemical technics there is a great deal lacking in our fundamental knowledge of the structure of the simplest cell of the body, the red blood cell. We know that the erythrocyte springs from the bone marrow as a relatively large flat cell, lithe and elastic, the so-called reticulocyte. As the red cell circulates through miles of capillaries it is constantly subjected to warping and distortion but promptly resumes its discoid shape when the stress is released. Gradually it manifests the conventional ageing process, i.e., "thickening about the middle," and as it becomes more spheroid it loses its elasticity so that threading the small capillaries becomes more hazardous and mechanically difficult. Many red blood cells fragment in the surge of the circulating blood while others find stagnation in the recesses of the spleen more to their liking and there pass to their oblivion by other physiological processes.

The average life of the erythrocyte is about 120 to 125 days. It has been estimated that the normal individual destroys 10,000,-

000 red cells per second. By such reckoning the carnage transpiring in this auditorium surpasses comprehension.

It would be most helpful in the study of the breakdown of the red cell if more were known regarding its detailed histology. Chemical analysis indicates that about 70 per cent of the cell mass is comprised of water, about 25 per cent is hemoglobin and only about 3.5 per cent represents the stroma.

It is the structure of the ströma which chiefly determines the shape of the erythrocyte. The stroma is composed of lipids such as lecithins, cephalins and sphingomyelins, and of a peculiar protein called "stromatin" which resembles collagen more than any other tissue substance found in the body. Much of this protein is not free but is combined with the lipids. Because of the relatively small amount of stroma in the cell it is necessary to assume the distribution of some of its constituents in organized molecular layers particularly at the surface. It has been calculated by Ponder and others that one protein molecule probably orients a mosaic containing about ninety lipid molecules. The lipids are chiefly arranged in monomolecular palisades, with the fatty acid poles directed centrally and the phosphoric acid-choline portion more or less facing the exterior surface. The proteins are probably arranged tangentially to the surface of the cells and are said to be more concentrated in the area of the disc concavities.

The interior of the erythrocyte is even less well understood. We know from the amount

of hemoglobin in the cell that the molecules must be very closely packed and heavily hydrated. In other words the hemoglobin is probably in the form of a gel. Whether the stroma permeates the cell is not known, but stromatin probably forms a gel readily, so that the most probable structure is one of strands of semiliquid protein material forming a matrix which in turn is conjugated loosely with the hemoglobin mass. That the normal red cell maintains its discoid shape is due not only to the unique organization of the stroma but also to a plasma albumin which is absorbed onto the surface of the cell.

Hemolytic agents operate by disturbing the intricate molecular organization of the stroma. Saponin, for example, when added in very dilute solutions to washed red cells first causes small discreet irregularities to appear on the surface of the erythrocyte, indicating a focal reaction of the hemolytic agent with certain groupings comprising the cell membrane. When the hemolysin is used in stronger concentration increasing numbers of crenation points appear until the entire surface is thickly studded. At the same time the erythrocyte tends to become more spherical and finally is transformed into a swollen, distorted sphere with a smooth surface. During the first phases of this process hemolysis may be prevented by washing off the saponin or by adding normal serum which neutralizes the hemolytic action of this and many other substances. The red cell then tends to return to its original shape. If, however, hemolysins are permitted to act until the red cell becomes a smooth sphere, the process becomes irreversible and the distended erythrocyte vanishes rather suddenly from the microscopic field. At that moment the hemoglobin which is confined in some kind of orderly arrangement within the cell rapidly flows out through the open pores and only a gossamer-like unit of stroma

("ghost") remains of the original structure. It is probable that most hemolytic agents, whether they be a saponin or a lipid solvent or a specialized protein fixed to the cell, disrupt the erythrocyte by this same mechanism of disorganization of the surface structures.

DR. SIDNEY C. WERNER: Can the hemoglobin leave the red blood cell without hemolysis in normal circumstances?

DR. HANGER: No, that is hemolysis. The clinical picture of hemolytic diseases is determined to some extent by the location within the body where red cell breakdown takes place. Hemoglobinemia is more prone to occur when the process is intravascular. On the other hand, when red cell destruction takes place within the spleen or bone marrow the liberated hemoglobin is taken up immediately by the contiguous cells and is transformed to bilirubin by intracellular processes. In these cases an acholuric jaundice rather than hemoglobinemia and hemoglobinuria is the rule. Normally 2 or 3 mg. per cent of hemoglobin is found in plasma due to mechanical fragmentation of red cells which is constantly taking place in the circulating blood. Under pathological conditions hemolysis may be so severe that three-quarters or more of the red cells of the body are destroyed within a few hours and large amounts of hemoglobin, exceeding 300 to 400 mg. per cent may appear in the plasma. In such cases a portion of the hemoglobin is excreted in the urine; another portion is taken up by the reticulo-endothelial system to be converted to bilirubin and some is transformed to hematin which at once combines with albumin to form "methemalbumin." Methemalbumin, a substance with a characteristic absorption spectrum recently described by Fairley, is relatively persistent in the blood stream since it is not excreted by the kidneys and is slowly absorbed by the reticulo-endothelial system.

When free hemoglobin in the plasma exceeds 135 mg. per cent it tends to appear in the urine and after levels exceeding 200 mg. per cent are reached, the amount of hemoglobin excreted by the kidneys is proportional to the blood level. In the lower ranges tubular re-absorption has been shown to play a rather important rôle. Hemoglobin, which has approximately the molecular weight of albumin, passes through the glomerulus about 3 per cent as readily as creatinine. When it occurs in the glomerular filtrate in amounts less than 2 to 3 mg. per cent none appears in the urine; above these levels, tubular reabsorption becomes inadequate and hemoglobinuria develops. If the tubules become injured by repeated exposures to hemoglobin and its derivatives, the reabsorptive power may become impaired; hence, in chronic hemolytic diseases hemoglobinuria may be observed when the blood levels are lower than 130 mg. per cent. Also, in the condition known as "march hemoglobinuria" a disturbance of tubular reabsorption must be assumed. Patients with this rare condition are usually young male adults who develop red or brownish urine after prolonged walking and running. The amount of blood destroyed during the episode has been shown to be negligible and except for hemoglobinuria symptoms are few. The condition is usually a temporary one and is of little clinical importance. Posture has been assumed to play a rôle in the red cell breakdown and in altering renal function but the disturbance has not been adequately explained.

We might turn now to the formation of bile pigments from hemoglobin. Dr. Stetten will review briefly for you the breakdown of hemoglobin and will trace the various derivatives through the reticulo-endothelial system, blood, liver and intestinal tract.

DR. DEWITT STETTEN, JR.: At the outset, I should like to call your attention to a

recent review by Watson,* which contains a critical discussion of many of the points to be covered in this clinic.

In addition to hemoglobin there are several biological pigments of the iron-porphyrin-protein type, among others catalase, some of the cytochromes and myoglobin. Other than the fact that myoglobin has been shown to contribute to the bile pigments, little is known of the catabolism of these compounds, but it may be supposed that the iron-porphyrin portion of these molecules is handled by the body in a fashion similar to that of hemoglobin.

The normal destruction of the vast majority of red cells occurs not in the free circulation but, as Dr. Hanger has indicated, in the reticulo-endothelial system. Of the three major portions of the hemoglobin molecule, we may speak with some assurance of the disposition of the protoporphyrin and of the iron, but we have very little information as to the intimate fate of the globin which in terms of weight is the major portion. The porphyrin nucleus, it will be recalled, comprises four five-membered rings of the pyrrol type bound to each other by carbon bridges, called methene bridges, of which the one designated α (Fig. 1) is of importance to the present discussion. About the periphery of the nucleus are several substituents, in the case of protoporphyrin, vinyl, methyl and propionic acid. The point of attachment to globin is according to some authorities over these propionic acid side-chains, while the iron always of the divalent or ferrous variety in normal hemoglobin is bound to the pyrrol nitrogen atoms, two by primary valence and two by coordinate valence. Whereas the porphyrins in general are extraordinarily resistant to oxidative ring rupture, the presence of an atom of iron in the center of the nucleus alters this stability and renders the ring system susceptible

* WATSON, C. J. Some newer concepts of natural derivatives of hemoglobin. *Blood, J. Hematol.*, 1: 99, 1946.

to oxidation even by such mild agents as H_2O_2 . This is the first step in the biological destruction of hemoglobin, the oxidation of the porphyrin at the α -methene group but without the elimination of either the iron or the globin. The green pigment which results

iron contained in the body is determined not by the rate of its excretion but by the rate of its absorption across the intestinal mucosa. This, in the normal animal, is very small but for reasons not well understood becomes vastly larger after hemorrhage. Since iron

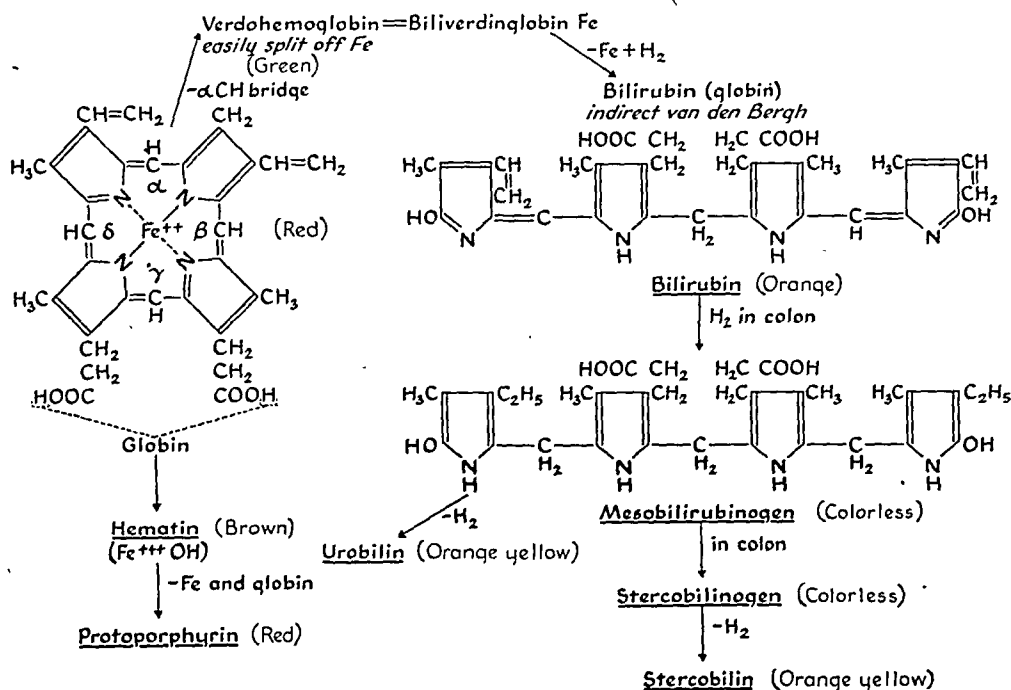


FIG. 1. Some of the more important natural derivatives of hemoglobin. (From WATSON, C. J. Some newer concepts of the natural derivatives of hemoglobin. *Blood, J. Hematol.*, 1: 99, 1946.)

has recently been called verdohemoglobin; it is normally present in red cells to a very appreciable extent and is familiar to all of you as the material formed from hemoglobin by *Streptococcus viridans*. It is characterized by the ease with which on treatment with dilute acid it may lose its iron, in contrast to hemoglobin in which the iron is more stably held. In fact, so easily does it lose its iron that this inevitably happens and we are left with biliverdin-globin.

At this point it will be well to review briefly the fate of the iron. You will remember that the body has no efficient method for getting rid of iron, that the iron lost per day except for such accidents as hemorrhage or hemoglobinuria is trivial. The quantity of

cannot be eliminated from the body it follows that the iron released by verdohemoglobin must be efficiently stored and re-utilized. Today the nature of this storage is fairly well understood. A curious protein, ferritin, occurs in the spleen and liver into the interstices of the lattice of which tremendous quantities of hydrated ferric oxide may enter without detectable alteration in the dimensions of the lattice. In fact, so much ferric oxide may enter this molecule as to bring its iron content close to 25 per cent; not only may it enter readily but it may leave just as easily. This reversible introduction of iron into ferritin, first demonstrated to occur *in vitro*, has recently been shown to occur in the living animal. Hepatic and

splenic ferritin, therefore, may be regarded as a warehouse for the transient storage of iron arising from the breakdown of verdohemoglobin and awaiting re-incorporation into fresh hemoglobin.

To return to the biliverdin, this is now reduced to bilirubin and for the biochemist it is impossible anatomically to localize this reaction. Practically every tissue that has been investigated seems to be capable of bringing it about and a wide variety of naturally occurring reductants, mostly breakdown products of glucose, serve as reagents. There is some reason to suspect that this reduction in the mammal is associated with glycolytic processes in the liver in that it apparently fails to occur when the liver is depleted of glycogen.

Bilirubin is a normal plasma constituent in concentrations of 0.25 to 1 mg. per cent. It occurs in two modifications which are currently called hemobilirubin and cholebilirubin. Hemobilirubin, which makes up the bulk of the normally occurring plasma pigment, is supposed to be the initial product and according to some authorities is still firmly linked to the original globin residue. It is non-dialyzable, does not cross the renal glomerulus and gives an indirect van den Bergh reaction. It is suggested that only in the liver is the pigment dissociated from its protein but whether by the Kupffer cells or the polygonal cells is not clear. The free pigment, as its ion, is normally injected into the bile. Should there be an obstruction to the bile flow, the bilirubin is regurgitated into the blood stream supposedly through the cells of the ampulla of the bile capillary. Once in contact with plasma proteins this regurgitated bilirubin now associates itself loosely with serum albumin with which it migrates. This, cholebilirubin, is characterized by dialyzing readily across both artificial and glomerular membranes and by the direct immediate van den Bergh reaction. Whereas the indi-

rect reacting pigment does not appear in the urine even when present in the blood in high concentration, cholebilirubin has a low renal threshold of 1 to 2 mg. per cent and appears regularly in the urine when this concentration in the blood is exceeded.

In the intestinal tract, probably because of the reducing action of the intestinal flora, bilirubin undergoes a series of hydrogenations which give a mixture of products, mesobilirubinogen and stercobilinogen; this mixture according to Watson is best referred to as urobilinogen. Urobilinogen is in part absorbed into the portal circulation but the normal liver effectively removes about 98 per cent from the blood and re-injects it into the bile. Some 2 per cent escapes the liver, travels into the systemic circulation and ultimately is excreted in the urine. Should liver function be impaired, the complement of urobilinogen escaping the liver and appearing in the urine may be expected to rise. The complete lack of urobilinogen in the urine is rarely seen except under conditions when bilirubin has been excluded from the intestinal tract. The last step in this reaction sequence is not a biological reaction at all but an autoxidation of urobilinogen, whether urinary or fecal, to give urobilin. This pigment like the foregoing turns out to be a mixture of two components, urobilin 9 α and stercobilin. The only importance of this reaction is the fact that the products do not give a color with Ehrlich's aldehyde reagent, the conventional test for urobilinogen, and therefore this test should be performed upon fresh specimens.

DR. HANGER: The reactions outlined by Dr. Stetten are of clinical and diagnostic importance. In hemolytic syndromes the amount of stool urobilin (stercobilin) may be enormously increased. The normal output of this substance in the stool in twenty-four hours rarely exceeds 200 mg. but in hemolytic jaundice this amount may be ex-

ceeded ten-fold. The stool urobilin excretion may be employed as a measure of blood breakdown. In anemic patients, however, absolute values may be misleading. For example, the excretion of 200 mg. of stercobilin in twenty-four hours by a person with a

TABLE I

FACTORS LEADING TO RED BLOOD CELL DESTRUCTION

1. Mechanical fragmentation
2. Spherocytosis
3. Fixation of specific globulins to red cell surfaces
4. Stasis
5. Splenic activity
6. Injury of cell by exogenous chemicals
7. Metabolic hemolysins

red blood cell count of 1,000,000 would be abnormally high and an indication of excessive blood cell breakdown in that individual. Another factor leading to erroneous interpretation is that in cases of violent hemolysis there frequently is considerable injury to the liver. Under these conditions, shock with focal necrosis of the liver is not uncommon and the jaundice that develops may be due in part to hepatic injury, with a direct van den Bergh reaction in the serum and bile appearing in the urine.

We will now consider some of the more common factors which promote the destruction of red cells. (Table I.) Reference has already been made to mechanical fragmentation which is probably the chief cause of red cell breakdown in the normal individual and to the development of spherocytosis which usually antecedes hemolysis.

Hemolysis may also be caused by certain globulins which may become attached to specific structures on the red cell surface. Some globulins are primarily injurious to the cell causing direct disruption of the structure; others "sensitize" by becoming fixed to the cell ("amboceptor") but the presence of "complement" is requisite for the occurrence of hemolysis. Even the attachment of amboceptor is said to increase the fragility of the sensitized red cells to mechanical stress and strain.

Other serum globulins are not directly hemolytic but are injurious to red cells by inducing agglutination (agglutinins). Clumping of erythrocytes causes them to rupture more readily in a shaking apparatus and presumably accelerates breakdown in the circulating blood.

Stasis of blood in the spleen is regarded by many as a factor leading to destruction of red blood cells in health and in disease. It has been pointed out that spherical cells and clumped cells especially tend to be enmeshed in the intricate vascular bed of that organ, where active phagocytosis of red blood cells can be demonstrated to take place. Studies by Dameshek and others suggest that in certain diseases the spleen may promote spherocytosis and increased red cell fragility. It is probable that actual contact of the red cell with the cells of the sinusoids rather than a secretion by the spleen is necessary for this action. Stasis, therefore, may be an important preliminary stage in the aging and elimination of the erythrocyte.

The chemical agents with hemolytic properties are very numerous and varied and will not be specifically enumerated here. Many of these substances which are highly lytic to washed red cells *in vitro* exert but little effect in the living organism because of the inhibiting action of serum. Conversely, a number of drugs such as sulfonamides and plasmochin (notably in the Negro race) which have but little intrinsic hemolytic activity may cause severe hemolytic anemia in particular cases. Some agents, such as phenylhydrazin and certain snake venoms, show hemolytic properties with predictable certainty but a large group produce symptoms only in persons with natural or acquired idiosyncrasies to that particular chemical. Favism is a form of severe hemolytic anemia common in certain Mediterranean regions and is caused by contact with the fava bean or vine. The disease

occurs primarily in those who manifest a sensitivity to certain products of the plant. The mechanism by which hemolysis is caused by drugs, bacterial toxins etc., in the body is not known but may involve injurious conjugation of the hemolytic agent or its derivative with the patient's cells, or the excitation within the organism of hemolytic processes which normally are held latent. The tissues themselves contain many products of metabolism which are potentially hemolytic, such as fatty acids, bile salts, soaps, lecithins and lysolecithins. The question is often raised whether under special conditions these naturally occurring substances may not be instrumental in breakdown of red cells. The lysolecithin theory is an attractive one, and I have asked Dr. West to discuss it for us.

DR. RANDOLPH WEST: The literature on lysolecithins was summarized to 1941 by Singer* and I refer you to his article on the subject. The first information was gained indirectly through study of cobra venom and allied snake venoms. The earlier work was done in 1860 by Weir Mitchell. In 1902, Flexner and Noguchi studied the phenomenon carefully and found that cobra venom would not bring about hemolysis of washed red blood cells and that the presence of serum was necessary for hemolysis. They then determined that cobra venom contained an enzyme which when acting on lecithin present in serum produced a form of lecithin which was lytic. From a study of snake venoms it was found that an enzyme and lecithins of serum produced a lytic lecithin which acted on red cells.

The problem was then carried on by Fahraeus who noted a difference in the sedimentation rate of blood from the splenic artery and from the splenic vein. The sedimentation rate was more rapid in

the splenic artery than in the splenic vein because lysolecithin inhibits rouleau formation.

Further studies were carried out defining the conditions under which lysolecithin was formed in serum. In summary, they are as follows: If blood be drawn and placed immediately in the icebox so that serum is separated at low temperatures, then that serum, if left to stand without stirring, will give rise on subsequent incubation at body temperature to a lytic form of lecithin which can be extracted by organic solvents and tested for hemolysis against washed red blood cells. That is the general technic for determining the lysolecithin content of serum.

Stirring decreased the amount of lysolecithin formed. An analogy exists with stagnant and circulating blood. Under conditions of complete stasis the action of the enzyme, which has many properties in common with complement, is much greater than when the blood is agitated.

This led to the theory that stagnant blood anywhere in the body, and particularly in the spleen, gives rise to an increased rate of production of lysolecithin which then might be a factor in hemolysis of red cells in the body. Studies reported on splenic artery and splenic vein blood and on blood from varicose veins, show a considerable increase in lysolecithin in stagnant blood over blood that is circulating rapidly in the general circulation. Lysolecithin, however, has not been demonstrated to act in the presence of plasma or serum and acts only on washed red blood cells, so its position as an active factor in bringing about hemolysis in disease of man is still open for further investigation.

DR. HANGER: Hemolysis in disease may depend upon one or more of the factors that have been discussed. In Table II these conditions have been arbitrarily separated into (1) those in which a demonstrable defect of the red cells may be significant, (2) those in

* SINGER, K. Lysolecithin and hemolytic anemia. The significance of lysolecithin production in the differentiation of circulating and stagnant blood. *J. Clin. Investigation*, 20: 153, 1941.

which a serological factor is either demonstrable or suspected and (3) those in which abnormal splenic activity (hypersplenism) is present.

In general, the symptomatology of the hemolytic state depends on the rapidity

TABLE II
HEMOLYSIS IN DISEASE

- A. Red Blood Cell Factors:
 - 1. Anoxia susceptibility
 - 2. Congenital spherocytosis
 - 3. Acid susceptibility
 - 4. Heat injury
 - 5. Malnutrition
 - 6. Idiosyncrasies to certain chemicals and drugs
 - 7. Parasitic infestations and bacterial infections
- B. Serological Factors:
 - 1. Naturally occurring agglutinins
 - 2. Specific antibodies to red blood cell agglutinogens
 - 3. Heterologous antibodies to red blood cells
 - 4. Cold agglutinins (reversible)
- C. Splenic Factors:
 - 1. "Hypersplenism"

with which blood is destroyed and whether the destruction takes place within an organ rich in reticulo-endothelial elements or free in the vascular system. Patients during brisk hemolysis often develop headache, extreme backache, abdominal pain and pains in the legs. There is frequently a chill followed by a rapid rise of fever; there may be vomiting and mental disturbances. The spleen often enlarges and may be tender. Within a few minutes or hours it will be noted that the urine is bright red or dark brown. In severe cases anuria develops rather quickly and there are often manifestations of shock, air hunger and signs of acute anemia. Rapid hemolysis is always a serious affair. One of the current misconceptions is that the anuria which develops is due primarily to the precipitation of hemoglobin by acid urine in the renal tubules and that alkali administration should be vigorously maintained until the urine becomes alkaline. At autopsy in these cases it is quite true that hemoglobin casts are often found in the tubules but recent investigations tend to indicate that crystalline hemoglobin is not toxic and

is not precipitated by acid urine. It is more probable that anuria in these cases is due to shock, secondary to decreased renal circulation. Hemoglobin casts are found in the tubules only when hemoglobin is administered after anuria has developed and are dependent upon, rather than the cause of, the urinary shutdown. It is true in animals with acidosis that the hemoglobin tends to break down into acid hematin and to methemoglobin which may be injurious to renal tubules but the necessity for alkalinizing the urine is probably not as important as is generally taught. Moderate doses of alkali are not contraindicated but excessive doses may be toxic and the alkalinity of the urine should not be used as the sole index of adequate therapy. The most important treatment of massive hemolysis is the prevention of shock and this is usually best attained by liberal parenteral administration of fluids, preferably transfusions. Some authorities raise the theoretical objection that the patient is destroying a great deal of blood and to give transfusions merely supplies more fuel for the flame. This objection is probably more theoretical than real and I repeat the important treatment of the hemolytic crisis is to maintain adequate blood pressure and adequate renal blood flow if possible.

DR. YALE KNEELAND, JR: I should like to pin you down specifically. If you see a case of black water fever with massive hemolysis, you do not believe it is necessary to give intravenous alkali. Is that correct?

DR. HANGER: According to the best information you do not poison your patient with alkali. You alkalinize mildly. It apparently is not the crucial thing. Recognizing that these anemias are violent and acute, I should say that transfusion and the supportive measures are probably the main factors.

DR. JOHN DEAN: Why should one alkalinize at all?

DR. HANGER: Chiefly on the basis of the observation that when acidosis occurs there tends to be formation of methemoglobin which apparently affects tubular function. It also diminishes the blood flow through the kidney.

DR. ROBERT F. LOEB: I do not believe that the British group who have studied black water fever will subscribe. I believe it is customary in black water fever to give massive doses of bicarbonate in one way or another. I think there is evidence to indicate that would make a difference.

DR. HANGER: To come back to Dr. Kneeland's question, I would give alkali but I would not regard it as the most important part of the therapy.

Among the hemolytic disorders in which a concomitant defect in the red cells is demonstrable is sickle-cell anemia. I have asked Dr. Turner to give us a brief survey of this problem.

DR. JOSEPH C. TURNER: In 1910, sickle-cell anemia was first described in this country by Herrick and it has been recognized since that time as an important type of hemolytic anemia in any community having a large number of negroes. The name itself carries perhaps the unjustifiable implication that the property of sickling is a sufficient explanation for the disease. While it is probably true that sickling is an important factor in pathogenesis, we do not know precisely how sickling is involved in the hemolytic process and what its relation may be to the various other pathological manifestations.

We may begin by considering the so-called sickling "trait." This, as you undoubtedly know, is found in the colored race all over the world, in Africa, North America and Central and South America in from 5 to 20 per cent of the population. It is inherited apparently as a dominant Mendelian character and the vast majority of people who bear it are healthy. Only in

perhaps 1 or 2 per cent does sickle-cell anemia develop. The anemia usually occurs early in life although we have seen patients in this clinic with the first manifestation of sickle-cell disease at the age of twenty-five or thirty. Death before middle age is the rule. Sickle-cell anemia has been described in the white race. Usually the people involved are Mediterraneans, Greeks, Sicilians or Arabs and one may suspect that at some time in the past there has been an admixture of negro blood. Such cases are extremely rare.

Sickling may be defined as a reversible distortion of the erythrocyte which occurs under lowered oxygen tension. The method ordinarily employed to demonstrate sickling is quite simple and I have no doubt you are all familiar with it. A drop of blood is placed on a slide, covered with a slip, sealed with paraffin and then placed in the incubator. The slide is examined microscopically at intervals of three hours or so.

The course of sickle-cell disease is extremely variable and may run from one to fifteen years. During this time a great variety of clinical manifestations may be encountered. One of the most curious is the leg ulcer, usually found around or just above the ankle. These ulcers are persistent and extremely difficult to treat. There may be rheumatic manifestations which simulate acute rheumatic fever almost precisely. Pains occur in and about a variety of joints and, moreover, one may find cardiac enlargement as well as systolic and diastolic or presystolic murmurs at the apex. Any negro suspected of having rheumatic fever should have his blood examined for the presence of sickling.

No less dramatic than these manifestations of the disease are those which are thought to be associated with changes in the small blood vessels in the shape of vascular thrombosis or circulatory stasis. One finds for instance neurological disturb-

ances. Since any area of the brain may be affected the symptoms vary from mere drowsiness to a fatal cerebral accident. In similar fashion bones may be involved. Areas of infarction occur which may be responsible for acute pain. These, if they involve the spine, may take the form of the common syndrome of lower back pain. We have seen a man here who entered with such a complaint and on x-ray examination he had an area of bone destruction in a lumbar vertebra. Such findings are presumably related to obliteration of nutrient arteries.

The most critical aspect of sickle-cell disease is the so-called abdominal crisis, which so frequently ushers in a fatal phase of the disease. Severe abdominal pain is usually accompanied by some muscular rigidity, in consequence, the clinical situation closely resembles a surgical condition of the abdomen and differential diagnosis may be extremely difficult. In sickle-cell disease such an abdominal crisis may be followed by a rapid destruction of blood with death in a matter of days or even hours. Shock is usually a significant part of hemolytic crises and must be treated vigorously.

So much for a brief view of the outstanding clinical manifestations. As for the pathological condition it is both curious and rather unsatisfactory. In children the spleen has been found enlarged but in adults this organ has frequently been almost destroyed—probably a manifestation of atrophy secondary to vascular thrombosis. The spleen may weigh only 10 or 15 Gm. Splenectomy, I should say, has not proved to be of any value in treatment.

The most interesting changes, interesting because they seem to be related to many of the clinical manifestations, are in the small blood vessels. These may be everywhere engorged and virtually occluded by what appear to be clumps of agglutinated sickle cells. They may, moreover, show an actual anatomical change in the vessel wall,

as thickening, intimal proliferation or tortuosity. All such changes could act to promote circulatory stasis and the physiological equivalent of thrombosis. An organized thrombus is not frequently seen pathologically. The findings, however, fail to account satisfactorily for what has happened in life and pathologists have sometimes been forced to conclude on examination only that the patient died of anemia.

We come now to the sickle cell itself, the phenomenon of sickling and its physical and chemical analysis. Sickling appears to be a property of the cell and not dependent upon the presence of serum. That is to say, if the cells are washed they still sickle. This does not imply, however, that there may not be substances in the serum which affect sickling. Indeed, there are substances of a non-specific sort that can influence sickling, such as bile salts and pH. If a preparation of washed cells is made in a chamber which is designed to permit evacuation of air and flushing of the system with gases, one finds that on removal of air and the substitution of an oxygen-free gas such as nitrogen, carbon dioxide or ethylene, sickling occurs in a few minutes. Then if, air or oxygen is re-admitted the cells spring back into normal shape instantaneously. Carbon monoxide is also capable of reversing the process of sickling and so it has been attractive to think that the process is associated with reduction of hemoglobin; it may be but the proof is wanting. We have examined hemoglobin prepared from sickle cells spectrophotometrically and can find in the absorption curves no abnormality.

It has been shown that the mechanical fragility of sickle cells is increased, but as yet we have no complete or satisfactory account of the relation of sickling to an increased rate of hemolysis.

As for treatment there is little to say. Oxygen has been employed over a period of one week to four weeks in an attempt to

alleviate the symptoms in sickle-cell crises. It appears that the number of sickle cells in venous blood is reduced as the result of such therapy but the process of hemolysis seems to be unaffected by the treatment. Transfusion has been employed, not only for the

TABLE III

	Sple- nectom- ies	Died fol- lowing Oper- ation	Died of Dis- ease	Died of Other Causes	Total Deaths
Congenital hemolytic icterus.	56	3	1	5	9
Idiopathic purpura.....	58	0	4	5	9
Banti's.....	96	11	28	4	43

shock which occurs in the acute crisis, but also in an attempt to hasten healing of the leg ulcers. It is difficult to say just how much transfusion will accomplish in such cases but our impression is that it is sometimes of benefit.

DR. HANGER: Another disease characterized by hemolytic anemia and abnormalities of the red blood cells is congenital spherocytosis. This is as much a surgical problem as a medical one and I have asked Dr. Elliott to discuss certain aspects of this disorder.

DR. R. H. E. ELLIOT, JR.: Congenital hemolytic icterus, or as it is more properly called, spherocytic jaundice can in most instances be completely arrested by removal of the spleen. It is in this particular blood dyscrasia that splenectomy has yielded its most brilliant results. The disease as will be remembered is characterized by jaundice, weakness, anemia and an enlarged spleen. The onset usually dates back to childhood and in most cases but not in all a familial history is obtainable. The characteristic blood findings in this disease are the presence of anemia, the presence of spherical microcytes, a reticulocytosis and increased fragility of the red cells.

Table III emphasizes the fact that in three groups of splenopathies in which splenectomy was performed in this clinic the

results have proved to be the most satisfactory in spherocytic jaundice. As will be noted, only one patient died of a recurrence of the disease as opposed to four in purpura. It is also worth calling attention to the fact that there were three deaths following operation. This is mentioned to stress the fact that the operation is obviously not without its hazards in certain instances.

In addition to the presence of jaundice and the various other clinical and laboratory findings previously described gallstones are also found in from 40 to 60 per cent of all cases. This is understandable when it is remembered that there is a tremendous amount of red cell destruction going on, particularly in the spleen, and that the pigment so released is carried directly to the liver where the increased excretion of the pigment in the bile may lead to the formation of stones. These stones are notably soft and in some instances can be crushed at the time of operation.

The results of splenectomy in atypical hemolytic icterus have been disappointing. We have collected information on eleven patients who have undergone this operation and five of these eleven are now dead of the disease. This does not necessarily mean, however, that splenectomy is contraindicated in this group. It has become the feeling in the Spleen Clinic that individuals who have an undiagnosed hemolytic anemia with a large spleen are entitled to splenectomy, provided examination of the bone marrow reveals no contraindication. Furthermore, it is believed that the presence of the spherical microcyte is in most instances necessary to the prediction of a satisfactory outcome after splenectomy. In other words, when the spherical microcyte is present the result will usually be favorable.

The one patient indicated in Table III as having succumbed to a recurrence of spherocytic jaundice after the spleen had been removed is worthy of mention. Similar

instances of recurrence have been reported in the literature. This particular patient was autopsied and the entire left upper quadrant of the abdomen found to be the site of multiple small nodules of accessory splenic tissue. Whether these were the result of the

briefly the experimental approach* used in this clinic a number of years ago in an attempt to elucidate the rôle of the spleen in this disease.

In 1936, Knisely,† who was studying the anatomy of the spleen, and in particular its

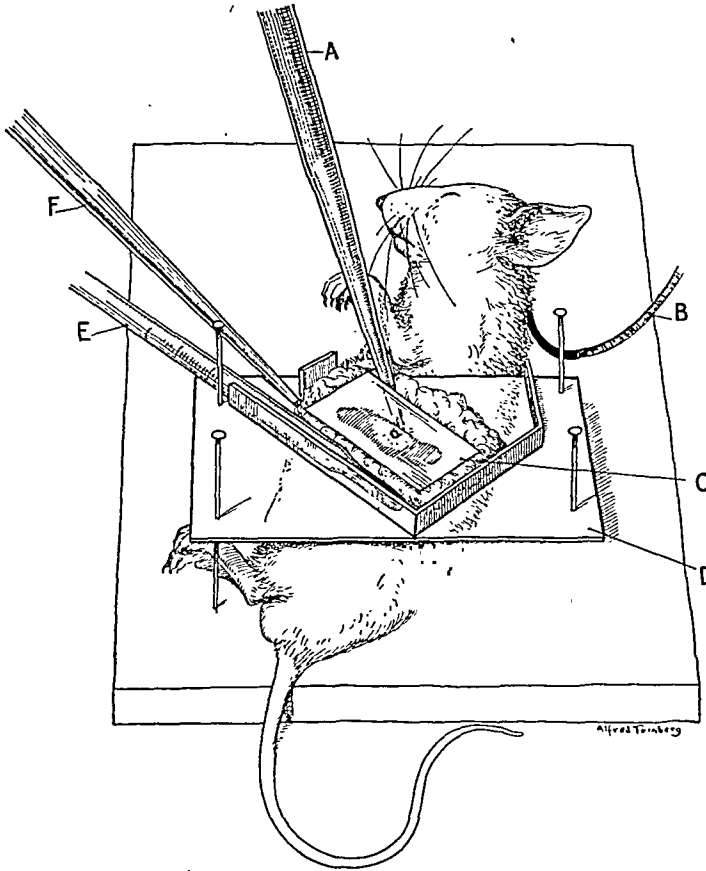


FIG. 2. Diagram of spleen chamber, as applied to the mouse. A, hollowtipped fused quartz illuminating rod; B, anesthesia tubing; C, cover slip roofing spleen chamber; D, celluloid table supporting spleen chamber; E, thermometer; and F, immersion fluid delivery tube. (From MACKENZIE, DAVID W., JR., WHIPPLE, ALLEN O. and WINTERSTEINER, MARGARET P. Studies on the microscopic anatomy and physiology of living transilluminated mammalian spleens. *Am. J. Anat.*, 68: 397, 1941.)

spillage of splenic tissue during operation or whether some accessory spleens had been left behind at operation is not known but both of these mechanisms have been suggested in the literature and do apparently occasionally occur.

It seems fitting at this juncture to mention

circulation, devised the technic of examining the living mammalian spleen depicted in

* MACKENZIE, D. W., JR., WHIPPLE, A. O. and WINTERSTEINER, M. P. Studies on the microscopic anatomy and physiology of living transilluminated mammalian spleens. *Am. J. Anat.*, 68: 397, 1941.

† KNISELY, M. H. Method of illuminating living structures for microscopic study. *Anat. Rec.*, 64: 499, 1936.

Figure 11. As can be seen the experimental animal, a mouse, has had its spleen exteriorized. Sodium amytal was used as the anesthetic agent. A fused quartz rod transmits a powerful beam of light through the thin edge of the organ which is then examined with a dissecting microscope brought down over a protective coverslip. Warmed Ringer's solution is used to prevent the spleen from drying out and to maintain a constant temperature.

This approach seemed to lend itself to a study of spherocytosis, a condition which is readily produced in the experimental animal by the use of a hemolytic serum. This serum was produced by injecting the washed red cells of a mouse into a rabbit. Subsequently, the anti-mouse red cell serum so formed was injected into the mouse's peritoneum. This produced spherical microcytes in profusion in the experimental animal and also induced enlargement of the spleen. When these spleens were examined microscopically they were found to bear a striking resemblance to the spleens of humans with hemolytic jaundice.

With the aid of the dissecting microscope it could be seen that the spherical microcytes so formed were unable to pass out of the pulp spaces of the spleen into the collecting veins and venous sinuses. They seemed to be almost selectively held back and did not have the elasticity that the normal erythrocyte had, which Dr. Hanger has previously mentioned. This would seem to explain why we find in the human more spherical microcytes in the pulp spaces of the spleen than in the splenic vein. It would also seem to explain, at least in part, the enlargement of the spleen in this disease and the reason why, after splenectomy, the spherical microcytes and therefore increased fragility persist throughout life despite the disappearance of the jaundice and other clinical manifestations of the disease.

DR. HANGER: Hemolysis may develop

under other clinical conditions in which an abnormality of the patient's red cells is demonstrable. A rare example is paroxysmal nocturnal hemoglobinuria (Marchiafava syndrome) in which the subject manifests hemoglobinuria after sleep but is relatively free of this symptom during the waking hours. Anemia is usually present and dysfunction may develop from the massive accumulation of hemosiderin in the epithelial cells of the kidney. The disease may run a progressively downhill course with increasing anemia terminating often with infection or with vascular thrombosis but may continue as a benign disorder for many years with unexplained remissions and relapses. Ham has demonstrated that the red cells in this syndrome tend to be lysed by normal plasma as well as by the plasma of the patient when the pH is lowered to 6.8. This effect can be attained by bubbling CO₂ through a tube of plasma containing the patient's cells. The cause of the symptomatology in man is not clear since the circulating blood probably does not attain this degree of acidity in the living body; furthermore, a thermolabile constituent of human serum is requisite for the phenomenon since hemolysis fails to take place when the patient's red cells are added to acidified heated serum. There is no cure for nocturnal hemoglobinuria but the symptoms are sometimes temporarily ameliorated by the administration of alkalis.

[The hemoglobinuria and jaundice that follow heat injury may also be attributed to an alteration of red cells. In severely burned subjects a certain number of erythrocytes become crenated and spherical due directly to the thermal injury. These cells tend to disintegrate quickly within the body.

In malnutrition and deficiency diseases increased fragility of red cells is not demonstrable by ordinary methods. Rhoads has found that erythrocytes obtained from dogs with black tongue are hemolyzed more

readily than normally by certain products of protein metabolism (indol), but it is not yet established that dietary factors play a similar rôle in any of the hemolytic anemia syndromes in man.

Certain micro-organisms, notably the plasmodia of malaria, may cause disruption of parasitized red blood cells. The destruction of erythrocytes in this disease is seldom of the abruptness or the magnitude to produce hemoglobinuria. Black water fever is a rare complication of chronic estivo-autumnal malaria treated with quinine, or rarely, atebine. It is a grave hemolytic disease more related to the hemolytic idiosyncrasies described above than to physical destruction of the red cells by the parasites. The hypothesis that serum at the time of the hemolytic crisis loses anti-hemolytic properties has not been substantiated. Bartonella infestation is also characterized by hemolytic anemia. Carrion's disease in humans is limited to a small region in the Andes but the recent studies of Pappenheimer on iron-containing bodies resembling bartonella found in the red cells of certain obscure anemias raises the interesting possibility that this type of infection may be more widely disseminated than is generally supposed.

The hemolytic action of certain serum constituents has already been mentioned. It is well known that in human bloods there are naturally occurring agglutinins A and B, upon which conventional blood grouping depends. These isohemagglutinins are found chiefly in the III-1 fraction of Cohn and may be concentrated from this component for diagnostic use. There are also rarer isoagglutinins and naturally occurring hemolysins, such as anti-M, anti-N, anti-P and anti-Rh factors, which are being intensively studied and amplified at the present time. Untoward effects such as capillary embolism and intravascular hemolysis tend to follow incompatible transfusions, espe-

cially when the recipient's serum contains agglutinins and hemolysins for the donor's cells. Constant vigilance in cross-matching of bloods must be maintained to avoid transfusion reactions and it must be borne in mind that occasionally hemolysins are present when agglutinins are absent.

Agglutinins and hemolysins may be present in the blood as true antibodies which develop following the injection of red cells containing a certain agglutigen. Complement is requisite for the demonstration of this type of hemolysis. Anti-A₂, anti-M, anti-N and anti-P may develop in human recipients receiving transfusions of cells with the appropriate antigen (agglutigen). More recently the Rh antigen (Rh₀ and its sub-groups Rh₁ and Rh₂) have been recognized as potential immunizing agents and a sensitizing hazard, to Rh negative recipients of Rh positive transfusions or to Rh negative mothers bearing Rh positive children. Erythroblastosis fetalis takes place when the serum of the mother containing anti-Rh factors passes the placental barrier in sufficient amounts to agglutinate and hemolyze the Rh positive cells of the fetus. Studies of the Rh factor lead to intricate biological concepts but from a practical aspect have already advanced fundamental knowledge of natural and induced hemolytic reactions as well as instigating life saving revisions of transfusion technics.

The origin of autohemolysins which Dameshek and earlier French workers have described in the blood of certain cases of acute spontaneous hemolytic anemia is obscure. Theoretically in the presence of certain conditioning substances ("Schleppers") a subject might immunize himself to some antigenic constituent of his own red blood cells and many authorities attribute the phenomenon of black water fever in chronic malaria to this mechanism. It is also possible in other instances that an individual

be sensitized to a complex antigen, such as the *Treponema pallidum* which fortuitously might contain a sensitizing grouping similar to one occurring in red blood cells. Paroxysmal (cold) hemoglobinuria could be explained by such an assumption. This disorder occurs usually in congenital syphilis and is characterized by the appearance of hemoglobinuria when the affected individual is subjected to chilling. An auto-hemolysin (immune globulin) is demonstrable in the serum of the patient which becomes fixed to the red cells only at relatively low temperatures but requires the presence of complement to effect complete hemolysis (Donath-Landsteiner test). In this disease cold is the precipitating factor for the immune reaction, but in most instances of acute hemolytic anemia the process of activation of the autohemolysis is not demonstrable. It is recognized by immunologists that specific antibodies of various types, such as typhoid agglutinins, gradually disappear from the circulating blood after infection but may re-appear after a variety of non-specific stimuli or intercurrent diseases. In a like manner latent specific hemolysin may be liberated from the tissues. Such a mechanism might be explained by the appearance of auto-hemolysins in the blood following intercurrent infections, allergic reactions, drug sensitivity and mild gastrointestinal upsets. At our present stage of knowledge, however, such assumptions have but little documented support.

It has been suggested that the cold agglutinins which appear so frequently during the late course of primary atypical pneumonia may promote hemolysis. Attempts have been made in this clinic and elsewhere to induce hemoglobinuria by chilling post-pneumonia patients with high titers of cold agglutinins but in no instances to my knowledge has hemolysis been observed.

Cold agglutinins may also be demonstrated in certain cases of idiopathic hemolytic anemia. In some of these instances, chilling of the patient may have deleterious effects.

The rôle of the spleen in the destruction of red cells in health and disease has already been mentioned. Hemolytic anemias are occasionally observed, in which one or more lytic processes are apparently enhanced by splenic activity. The term "hyper-splenism" is being employed more and more to denote dyscrasias of this type. Frequently the spleen is enlarged and is the site of local disease such as tuberculosis, syphilis, giant-cell sarcoma, Hodgkin's disease or non-specific inflammatory changes (reticulo-endotheliosis) and it is assumed that in these disorders there is irritation and augmentation of splenic function. Symptomatic relief is afforded by splenectomy in some of these cases. Splenectomy should be considered a desperate therapeutic measure in acute hemolytic syndromes which persist despite transfusions and other supportive measures. Operation has proved successful even in cases with considerable hemolysins in the serum and may be justified by the assumption that splenic activity is an accessory factor in the total hemolytic picture.

STUDENT: What is Lederer's anemia?

DR. HANGER: It is a name applied to a febrile hemolytic syndrome characterized by severe hemoglobinemia with hemoglobinuria and a rapidly progressive anemia which develops suddenly in children and young adults. The condition is probably not a clinical entity. Autohemolysins may be demonstrated in the blood in some cases. It is important to remember that the hemolytic process may be terminated by the administration of normal blood. Patients with Lederer's syndrome may present an alarming picture but the outcome is often favorable if transfusions are promptly instituted and maintained.

SUMMARY

The normal mature red blood cell is a pliable biconcave disc composed of hemoglobin (25 per cent), stroma (3.5 per cent) and water (70 per cent). The arrangement of these elements in the cell is not well understood. Ordinarily, the life of an erythron is approximately 120 days and about 10,000,000 red cells are destroyed every second. Hemolysis may be said to exist when the normal rate of red blood cell destruction is increased. Although many agents may be responsible for hemolysis it is probable that, like saponins, all depend upon disruption of the cell membrane for their effect.

When hemolysis occurs rapidly, particularly if it be intravascular, free hemoglobin appears in the plasma above the normal concentration of 3 mg. per cent. Above levels of 135 mg. per cent, it appears in the urine. If tubular reabsorption is impaired hemoglobinuria may exist with considerably lower plasma levels. Usually, however, red cell destruction occurs in the reticulo-endothelial system with the conversion of the hemoglobin to bilirubin and, when excessive, with the production of acholuric jaundice.

The breakdown of hemoglobin begins with oxidative ring rupture at the α -methene group of the porphyrin fraction of the molecule, resulting in a green compound called verdohemoglobin. This loses its iron, which is stored in the form of hepatic and splenic ferritin, and becomes biliverdin which on reduction is called bilirubin. Bilirubin exists normally in concentrations of less than 1 mg. per cent in the serum and may be subdivided into two fractions: hemobilirubin and cholebilirubin. The former retains its globin, is non-dialyzable, does not pass the glomerular filter, produces the indirect van den Bergh reaction and represents the larger fraction. The latter is free of globin but is associated with plasma

albumin and appears in urine when its concentration in the plasma exceeds 2 mg. per cent. In the intestinal tract bilirubin is further reduced to urobilinogen, part of which is absorbed into the portal circulation where it is almost entirely cleared by the liver and re-introduced into the bile. In the presence of impaired liver function, however, more than the usual 2 per cent of the portal bilirubin may elude the liver and gain access to the general circulation and so appear in the urine in increased amount.

Table I summarizes the usually recognized causes of red blood cell destruction while Table II attempts to classify these mechanisms as they occur in disease states.

How incomplete is our understanding, however, of the basic mechanisms of hemolysis is well illustrated in the case of sickle-cell anemia where a clear-cut abnormality of the red cell exists without obvious relation to the hemolytic process and where a rational form of therapy appears to have no effect. On the other hand, the excellent results obtained by splenectomy in congenital hemolytic icterus are seen to have some experimental foundation.

The clinical picture of chronic hemolysis is characterized by icterus, frequent enlargement of the spleen, anemia, leukocytosis and increase in reticulocytes. The urine is ordinarily free of bile although this is not invariable. The serum bilirubin is increased and classically gives an indirect van den Bergh reaction. Urobilin is increased in the stool and urobilinogen is usually present in the urine in abnormal amounts. If the liver is damaged, however, many of these points in differential diagnosis are of no value. Therapy is often disappointing unless some specific infection can be treated, some harmful agent be removed or splenectomy be advised. The success of the latter procedure is largely

limited to familial hemolytic jaundice although occasional excellent results are obtained in acquired hemolytic icterus and localized disease of the spleen.

Acute hemolysis presents quite a different and more serious prospect. The sudden onset is distinguished by headache, backache and leg pains. Pain in the abdomen may be severe and mimic an acute surgical abdomen. Chills and fever are common; shock, with anuria, may supervene. Anemia

and hemoglobinemia are found. Hemoglobinuria may be present in severe cases or when tubular re-absorption is defective. Transfusion is the treatment of choice since it tends to overcome the anemia, correct the shock and so increase renal blood flow. In some instances it apparently arrests the hemolytic process as well. Alkalinization of the urine remains good therapy though perhaps of secondary importance in preventing anuria.

Diabetes, Hepatomegaly and Splenomegaly^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a sixty year-old white, married, investment banker who entered the Barnes Hospital for the first time on the Surgical Service in July, 1924, because of recurrent attacks of abdominal pain. The family history revealed that one half-brother had diabetes. The findings of interest on this first admission were that the patient weighed 238 pounds and that his blood pressure was 158/100. Two urine specimens were negative for sugar. An appendectomy was performed and recovery was uneventful.

He reentered the hospital on June 11, 1946, complaining of weight loss, frequency of urination and glycosuria. Ten years before his second admission a cataract was discovered in the left eye; it developed very slowly thereafter. Six years prior to entry he developed mild substernal pain which radiated down the left arm; he was seen by a cardiologist who told him that he had no heart disease. At that time roentgenograms of the gastrointestinal tract were negative.

The patient had learned to test his own urine for sugar years before admission and stated that for more than twenty years glycosuria had occurred intermittently without any other symptoms. Two months before the second admission he began to lose weight rapidly and he noted increased frequency of urination. One month later glycosuria became persistent and two weeks

prior to entry he was seen by his physician who found the fasting blood sugar to be 263 mg. per cent. He was given a regulated diet and was advised to enter the hospital. The patient had taken moderately large amounts of alcohol for a number of years.

On admission, physical examination revealed the temperature to be 37°C., pulse 84, respirations 12 and blood pressure 110/68. The patient weighed 161 pounds. He was well developed and not acutely ill but showed evidence of recent weight loss. A partial cataract was noted in the left eye; both pupils reacted to light and accommodation. There was moderate arteriolar narrowing of the retinal arteries and some arterio-venous nicking. Examination of the upper respiratory tract was entirely negative. The lungs were clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular and there were no murmurs; the second aortic sound was accentuated. The abdomen was protuberant. The liver edge was easily palpable 10 cm. below the right costal margin and was described as smooth and tender. The splenic tip was felt 2 cm. below the left costal margin. Vibration sense was diminished and there was hypesthesia to pin prick over the dorsum of each foot.

Laboratory studies were as follows: Blood count: red cells, 4,510,000; hemoglobin, 13.3 Gm.; white cells, 5,900; differential count: eosinophiles, 3 per cent; stab forms,

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

17 per cent; segmented forms, 45 per cent; lymphocytes, 32 per cent; monocytes, 3 per cent. Urinalysis: specific gravity, 1.026; albumin, negative; sugar, 3 plus; sediment, negative. Blood Kahn reaction: positive; quantitative Kahn test, 4 Kahn units; Kolmer-Wassermann test, negative. Stool: guaiac negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; sugar, 145 mg. per cent; total protein, 5.5 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 2.4 Gm. per cent; cephalin-cholesterol flocculation test, 2 plus; brom-sulfalein dye retention, 40 per cent in thirty minutes. Oral hippuric acid test: 50 per cent excretion as Na benzoate. Corrected sedimentation rate: 0.8 mm. per minute. Basal metabolic rate: plus 13. Electrocardiogram: T wave inverted in lead I; Q wave present in leads II, III and CF IV; S-T segment depressed in lead II; left axis deviation. Roentgenogram of the chest: "The cardiac silhouette is at the upper limit of normal. The left ventricle appears to be somewhat prominent. The hilar shadows are accentuated. The lung markings are coarse and extend far out into both fields." Gastrointestinal series: "Indeterminate." Oral cholecystograms: "Normal gallbladder."

On admission the patient was given a diet of 200 Gm. of carbohydrate, 150 Gm. of fat and 80 Gm. of protein. A mixture of 15 units of protamine zinc insulin and 30 units of regular insulin was given before breakfast. Choline chloride, skimmed milk, and intensive vitamin therapy were also prescribed. Because of persistent glycosuria the insulin dosage was increased so that the patient was taking a mixture of 85 units of regular and 35 units of protamine zinc insulin daily. On this schedule blood sugars were as follows: fasting, 79 mg. per cent; 11:00 A.M., 126 mg. per cent; 4:00 P.M., 167 mg. per cent. The urine sugar decreased to an occasional trace.

Four days after admission the patient developed sharp pain in the right upper quadrant and his temperature rose to 38.7°C. The pain was described as radiating through to the back and was relieved by codeine and aspirin. No changes were noted at this time in the physical findings. Further laboratory studies were as follows: white cells, 6,250; corrected sedimentation rate, 1.4 mm. per minute; Van den Bergh test: direct, 0.72 mg. per cent; indirect, 0.8 mg. per cent; D-I ratio, 81 per cent.

The patient continued to have fever for the next ten days with frequent elevations to 39°C. His diabetes was difficult to control during this period and he had repeated insulin reactions. The temperature then fell to levels just above normal and the patient's condition improved. During the febrile episode he had had no jaundice or leukocytosis and the size of the liver and spleen had not changed. He was discharged on July 2, 1946, to return to the care of his private physician.

He did well for two weeks; he then developed profound anorexia, daily temperature elevations to 99° or 100°F. and increasing weakness. His appetite became so poor that he took nothing but orange juice by mouth and his daily insulin requirement was reduced considerably. Bilateral calf tenderness and extreme hypersensitiveness of the soles of the feet appeared, and the patient entered the hospital for the last time on August 2, 1946.

On admission, his temperature was 37.2°C., pulse 96, respirations 18, and blood pressure 142/88. He weighed 152 pounds. The significant changes from the physical findings previously recorded were as follows: a soft blowing apical systolic murmur was audible; the liver edge extended to the umbilicus and was quite tender; the spleen was questionably enlarged; the deep tendon reflexes were hypoactive and the soles of the feet were extremely painful to touch.

The laboratory findings were as follows: Blood count: red cells, 4,450,000; hemoglobin, 13.7 Gm.; white cells, 8,700; differential count: eosinophiles, 3 per cent; stab forms, 12 per cent; segmented forms, 53 per cent; lymphocytes, 26 per cent; monocytes, 6 per cent. Urinalysis: specific gravity, 1.015; sugar, trace; sediment, negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 18 mg. per cent; icteric index, 3.7 units. Stool: guaiac negative. Prothrombin time: 93 per cent of normal. Electrocardiogram: "myocardial damage of the coronary type."

A Levine tube was passed and the patient was given eight feedings daily of a mixture consisting of 200 Gm. of protein, 300 Gm. of carbohydrate, and 75 Gm. of fat. Large amounts of vitamin B complex were added to the feedings and the patient was given an insulin mixture containing 20 units of protamine zinc and 60 units of regular. The fractional urines consistently showed large amounts of sugar and the insulin was increased until on the fifteenth day the patient was taking a mixture of 117 units of regular insulin and 48 units of protamine zinc insulin. On this dosage the urine became sugar free for the first time. During this period the patient had been essentially afebrile, his weight had remained stationary and the liver had not increased in size. Shortly after the peak of insulin dosage was reached, he began to have frequent reactions and the amount had to be decreased rapidly.

Laboratory studies at this time were: total protein, 4.4 Gm. per cent; albumin, 2.5 Gm. per cent; globulin, 1.9 Gm. per cent; calcium, 7.3 mg. per cent; phosphorus, 2.6 mg. per cent; alkaline phosphatase, 14 Bodansky units; carbon dioxide combining power, 60 volumes per cent; serum chloride, 81 milliequivalents/liter.

On the twentieth hospital day râles were heard at both lung bases. The heart was

enlarged to percussion, the left border of dullness being at the anterior axillary line. One plus sacral edema and signs of ascites appeared. A repeat electrocardiogram showed little change. The patient was digitalized but signs of cardiac insufficiency persisted and he developed severe hiccoughs, often induced by palpation of the liver; they were unrelieved by sedation, atropine and carbon dioxide inhalation. Although his diabetes remained well controlled, he gradually became disoriented and then stuporous. During the last two weeks of life, the temperature gradually rose to a maximum of 40.8°C. and was unaffected by penicillin. The patient's course was steadily downhill. Cheyne-Stokes respirations were noted, the heart sounds became muffled and sacral and pretibial edema increased. Muscle twitching occurred but a Chvostek sign could not be elicited. Large doses of calcium lactate were given without effect. Sulfadiazine therapy was instituted and twelve hours later the temperature began to fall gradually. The patient's general condition showed definite improvement and on the day of death he seemed much better. That night, however, he suddenly became pulseless and despite emergency measures he expired quietly on September 1, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is extremely interesting and extremely complicated. For over twenty years the patient had had intermittent glycosuria, but until two months before the onset of his fatal illness, he had gotten on quite well. Suddenly the signs and symptoms of diabetes became prominent; that is, his glycosuria increased, frequency of urination appeared and marked weight loss occurred. It is well to inquire, therefore, whether such a chain of circumstances represents the effects of some important precipitating factor. Dr. Fletcher, will you comment on this point?

DR. PALMER H. FUTCHER: Frequently when a patient with asymptomatic glycosuria or mild diabetes suddenly develops the symptoms and signs of severe diabetes, there is a precipitating cause and, under such circumstances, one thinks of concurrent disease, particularly infection. However, occasionally an increase in the severity of diabetes occurs without a demonstrable cause.

DR. ALEXANDER: In this case there was a noteworthy finding on the second admission, namely, hepatomegaly. The liver was described as being tender and smooth and impairment of liver function was indicated by significant bromsulfalein retention and a two plus cephalin-cholesterol flocculation test; on the other hand, the hippuric acid excretion was normal and so were the total and fractional proteins. Dr. Wade, would you suggest the nature of the liver involvement, if indeed there was disease of the liver?

DR. LEO J. WADE: The only finding that suggests that this patient may have had a diffuse lesion of the liver is the bromsulfalein dye retention, but in view of the fact that the oral cholecystograms showed satisfactory dye concentration, I am skeptical of that result. I suspect that the most likely explanation for this single abnormality in liver function is a focal lesion of the liver, either infectious or neoplastic in origin.

DR. ALEXANDER: How do you interpret the two plus cephalin-cholesterol flocculation test? Is that equivocal?

DR. WADE: I think it is probably significant although a two plus cephalin-cholesterol flocculation test may occur in the absence of clinically obvious liver disease and under such circumstances no lesion may be found at autopsy to explain the abnormality. The alkaline phosphatase of 14 Bodansky units subsequently reported in this patient is compatible with a focal lesion of the liver and the absence of jaundice is not incompatible.

DR. ALEXANDER: Dr. Scheff, do you have any suggestions?

DR. HAROLD SCHEFF: I do not believe that cirrhosis of the liver can be ruled out.

DR. WADE: I would still be inclined to disregard the bromsulfalein retention in the absence of any other confirmatory test. The hippuric acid excretion does not suggest hepatic impairment.

DR. ALEXANDER: Forty per cent dye retention would seem to be a rather high figure.

DR. WADE: I have seen errors of this magnitude. Sometimes the amount of dye injected is excessive and occasionally the results are calculated incorrectly.

DR. ALEXANDER: Assuming the bromsulfalein retention is incorrect, and considering the two plus cephalin-cholesterol flocculation test and the elevated alkaline phosphatase, do you think that Dr. Scheff's suggestion of early cirrhosis may be correct?

DR. WADE: I do not believe so. At no time did the patient have anemia and normal total and fractional proteins would be unusual in a patient with cirrhosis. Cirrhosis is suggested by the dietary history but, of course, many individuals with a dietary history such as this man's do not develop cirrhosis.

DR. ALEXANDER: Could the large liver be explained on the basis of fatty infiltration such as is seen in association with diabetes?

DR. WADE: That is possible, but in such an instance I believe that the serum albumin would be decreased and that anemia would be present.

DR. SCHEFF: Splenomegaly is not seen in association with fatty infiltration of the liver.

DR. ALEXANDER: I agree that fatty infiltration *per se* would not explain the enlarged spleen.

DR. FUTCHER: In regard to the possibility that depressed liver function was as-

sociated with the fatty infiltration which occurs in diabetes, it is of interest to note the recent series of cases reported by Gray, Hook and Batty* who studied liver function in a number of patients with diabetes using the serum colloidal gold reaction. In those patients with severe diabetes the test was positive in 50 per cent of the cases. Dr. Wade has mentioned that a focal lesion may have been present here. I should like to ask specifically what type of lesion would lead to such marked hepatomegaly.

DR. WADE: During his hospital stay the patient had abdominal pain suggestive of that occurring with cholelithiasis.

DR. DONALD S. BOTTOM: The concentration of dye seen in the cholecystograms is not very great but there is a very definite gallbladder shadow. In our experience we would say that there is a 70 per cent probability that the gallbladder was normal.

DR. ALEXANDER: Is it possible that this man had thrombophlebitis of the portal system at the time of his attacks of abdominal pain which led to his appendectomy in 1924 and of which subsequently there was recrudescence which gave rise to focal infection in the liver?

DR. WADE: I think the time interval is much too long.

DR. ALEXANDER: When the liver was palpated, the patient frequently developed hiccoughs. This suggests a lesion involving the diaphragm. Dr. Moore, do you have any suggestions?

DR. CARL V. MOORE: Considering only the clinical picture here it seems evident that the liver enlarged rapidly and that the tenderness was due to stretching of Glisson's capsule. Diaphragmatic irritation indicates enlargement upward as well as downward. I believe carcinoma of the liver,

either primary or secondary, must be considered.

DR. ALEXANDER: Dr. Bottom, was the right diaphragm high?

DR. BOTTOM: It was slightly higher than the left diaphragm as is usually the case in normal subjects.

DR. W. BARRY WOOD, JR.: Most of the diagnostic suggestions considered so far do not explain the enlarged spleen. I should like to know how the spleen felt and just how large it was.

DR. WILLIAM H. OLMSTED: It was fairly firm and easily palpable below the costal margin.

DR. ALEXANDER: May not the spleen be enlarged in the presence of portal obstruction?

DR. WOOD: If the portal circulation is involved, the spleen as well as the liver is often affected. This point favors Dr. Scheff's suggestion of cirrhosis. If cirrhosis of the liver is to be considered, the fact that this patient also had diabetes suggests the possibility of hemochromatosis. However, there is no description of skin pigmentation.

DR. ALEXANDER: In hemochromatosis is not the liver smooth?

DR. OLMSTED: Yes, it is enlarged but usually quite smooth.

DR. WOOD: Is tenderness a prominent feature?

DR. OLMSTED: In the cases which I have seen the liver was not tender.

DR. WOOD: The presence of tenderness seems to me to mitigate strongly against hemochromatosis.

DR. ALEXANDER: What is the incidence of hemochromatosis without pigmentation of the skin?

DR. HENRY A. SCHROEDER: Approximately 20 per cent of patients with hemochromatosis do not have pigmentation of the skin.

DR. BERTRAND Y. GLASSBERG: The patient's diabetes was fairly well controlled

* GRAY, S. J., HOOK, W. and BATTY, J. L. Liver function studies in diabetes mellitus. *Ann. Int. Med.*, 24: 72, 1946.

during his hospital stay. In controlled diabetes hepatic enlargement is not common.

DR. ALEXANDER: That is especially true in patients given choline and other indicated therapy.

DR. SCHEFF: Is not fatty infiltration unusual in an older diabetic?

DR. OLMSTED: Yes.

DR. ALEXANDER: We now have suggestions of a focal lesion such as carcinoma, of cirrhosis and of hemochromatosis. It would be well now to mention the neurologic findings which were recorded. The patient had hypesthesia, paresthesias and later muscle tenderness and hyperesthesia over the feet. The reflexes were hypoactive.

DR. GLASSBERG: It has been pointed out that in carefully studied diabetic patients approximately 90 per cent exhibit some neurologic signs and these are often relieved by large doses of the vitamin B complex.

DR. OLMSTED: In my experience the neurologic symptoms are difficult to relieve.

DR. RAY D. WILLIAMS: I would agree. Large doses of B complex may sometimes help but they exert no specific effect. When the diabetes is controlled, improvement usually occurs. Cirrhosis has been mentioned as a possible diagnosis and it should be pointed out that although similar neurological findings are seen in cirrhotics, a high vitamin intake does not alleviate the complaints.

DR. ALEXANDER: The term "diabetic tabes" may be applied to a clinical picture such as the one exhibited here. However, there was also a positive Kahn test which brings up the possibility of syphilis. Subsequently the Kolmer-Wassermann test was negative and a quantitative Kahn test was reported as only four units. Dr. Clark, do you believe that a diagnosis of syphilis is justified?

DR. E. GURNEY CLARK: No, I think there is insufficient evidence for that diagnosis. A lumbar puncture was not per-

formed, however, and valuable data would have been obtained from that procedure.

DR. ALEXANDER: Dr. Wade, do you believe that syphilitic involvement of the liver could give rise to the signs observed here?

DR. WADE: I think that is most unlikely.

DR. ALEXANDER: The description of the liver is not that of *hepar lobatum*. Further, in the late stages, the syphilitic liver is usually small.

DR. FUTCHER: Fever has been reported as an accompaniment of syphilis of the liver, but I do not know how well substantiated that observation is.

DR. VIRGIL C. SCOTT: About 12 to 15 per cent of patients with cirrhosis have low grade fever. In regard to syphilis of the liver, this patient received large amounts of penicillin which should have led to a satisfactory response had syphilis been the responsible factor.

DR. ALEXANDER: On the patient's second admission it is interesting to note that the total blood protein had fallen to 4.4 Gm. per cent, although the albumin-globulin ratio remained normal. The calcium likewise fell to 7.3 mg. per cent and muscular twitchings were noted. Dr. Fletcher, do you believe that the fall in protein was responsible for the lowered calcium?

DR. FUTCHER: I think that that is entirely possible. If one attempts to explain the twitchings on the basis of hypocalcemia, however, it should be pointed out that no Chvostek sign was elicited.

DR. GLASSBERG: The low calcium would seem to be less important in view of the fact that the phosphorus was not elevated.

DR. ALEXANDER: Your point is well taken, in that when the calcium falls, the phosphorus usually rises. Dr. Fletcher, how do you explain the low serum chloride?

DR. FUTCHER: I am unable to do so particularly since there is no evidence of renal disease.

DR. ALEXANDER: Dr. Massie, on the basis

of the electrocardiograms and the signs of cardiac insufficiency, what changes would you expect in the heart?

DR. EDWARD MASSIE: Certainly the patient had severe coronary artery disease as indicated by the electrocardiographic pattern. The terminal cardiac failure may likewise have been on this basis. It is further possible that the patient had a myocardial infarction shortly before death but this cannot be stated with any degree of certainty.

DR. ALEXANDER: Are there further suggestions?

DR. OLMSTED: Untreated diabetics are apt to have infection of various types.

DR. GLASSBERG: Tuberculosis particularly should be considered here.

DR. ALEXANDER: The patient had unexplained fever which did not respond to penicillin; in addition, there was hepatosplenomegaly. Tuberculosis is certainly a worth while suggestion.

DR. WOOD: Tuberculosis is a definite possibility. Fever without leukocytosis is compatible with that diagnosis and it is well to point out that miliary tuberculosis may sometimes be extremely obscure.

DR. SCHEFF: How would tuberculosis explain the severe abdominal pain?

DR. ALEXANDER: Perihepatitis perhaps might have been responsible.

DR. SCHROEDER: The occurrence of heart failure in a patient with a poor dietary history also suggests the possibility of beriberi heart disease.

DR. ALEXANDER: In summary, this case presents a very difficult diagnostic problem. The patient had rather severe diabetes, probable diabetic neuritis, hepatosplenomegaly and fever. Among the explanations suggested for the hepatomegaly have been carcinoma of the liver, early cirrhosis and hemochromatosis. It is believed that the patient had cardiac failure probably due to coronary artery disease, possibly influ-

enced by thiamine deficiency. Tuberculosis, perhaps miliary in distribution, may have explained the rapidly fatal course.

Clinical Diagnosis: Diabetes mellitus; diabetic neuritis; hepatomegaly and splenomegaly due possibly to carcinoma, cirrhosis, or hemochromatosis, and tuberculosis.

PATHOLOGIC DISCUSSION

DR. JAMES O. BOLEY: At autopsy 50 cc. of fluid were present in the right pleural cavity and 25 cc. in the left pleural cavity. The heart was enlarged, weighing 610 Gm., and over the left ventricle there were depressed areas and thickening of the pericardium. On section these areas and the underlying muscle showed a large amount of fibrous tissue replacement. The myocardium varied in thickness from 5 to 16 mm. There was a healed infarct in the wall of the left ventricle measuring 6 by 8 cm. and extending into the interventricular septum to a distance of 3.5 cm. The coronary arteries showed advanced arteriosclerosis with marked narrowing of the left coronary. There was also advanced arteriosclerosis of the aorta. There were scars in the apices of both lungs and adhesions at the left apex. The lungs weighed 1,500 Gm., were firm and nodular and on cut section contained elevated reddish-gray areas. In the pleura near the right lower lobe, there was a calcified nodule 3 mm. in diameter, and there were also calcified nodules in the tracheobronchial and pulmonary lymph nodes.

The abdomen contained 1,200 cc. of fluid. The pancreas weighed 160 Gm. and was grossly normal. The kidneys together weighed 485 Gm.; the capsules stripped with little difficulty revealing yellowish-red, finely granular surfaces. An occasional small reddish-gray nodule was seen in the cortex.

The right adrenal gland weighed 48 Gm.,

the left 16 Gm. They were separated from the surrounding tissues with difficulty. Both were firm; on cut section the substance was rubbery, gray and translucent with occasional areas of caseation and foci of hemorrhage near the periphery. The changes were more extensive in the left adrenal than in the right.

The liver, which was yellowish-red in color, weighed, 2,930 Gm. On section the substance was mottled and occasional small gray nodules, up to 2 mm. in size, were noted.

The spleen weighed 660 Gm. A healed infarct was present. On section the substance was firmer than normal; the Malpighian bodies were increased in number and some were yellowish in color instead of gray. There was no generalized lymphadenopathy.

DR. MARGARET G. SMITH. We shall present the microscopic sections* in two parts, the first illustrating the vascular disease, and the second, the infectious process.

Figure 1 is a section of the descending branch of the left coronary artery, illustrating the marked arteriosclerosis and narrowing of the lumen. A section from one of the scarred areas (Fig. 2) shows a very old infarct with complete replacement by fibrous tissue. There were no changes suggesting recent infarction.

Sections from the pancreas revealed focal areas of interstitial fibrosis and hyalinization of most of the islands. In the kidney the changes of moderate arteriolar nephrosclerosis were seen.

Figure 3 is from the left adrenal and shows a large caseous area which extends to the fibrous capsule. There is infiltration by mononuclear cells, chiefly lymphocytes. In Figure 4, which is taken from the right adrenal gland, the process is seen to

be less advanced. There are areas of caseous necrosis and, surrounding them, degeneration of cells of the adrenal and an accumulation of very large mononuclear cells. In Figure 5 granulomatous lesions with large mononuclear cells, suggestive of the epithelioid cells of tubercles, are seen. Surrounding these are zones of lymphocytes. A higher power view from this area (Fig. 6) shows a number of the large irregular mononuclear cells containing encapsulated organisms characteristic of *Histoplasma capsulatum*. In Figure 7 a low power view is seen; it does not show the characteristics of the organism but indicates the large numbers present. Another section (Fig. 8) taken from the capsule of the adrenal shows a proliferative type of lesion with miliary granulomas resembling tubercles.

The section pictured in Figure 9 is from the liver. Although in the gross only a few granulomatous lesions were seen, they are extremely numerous on microscopic examination and are seen in almost every field; some are circumscribed and some are seen in the portal spaces. They vary considerably in appearance, some having only a few large epithelioid cells loosely arranged with many lymphocytes, while in others the epithelioid cells are compactly arranged with a multinucleated giant cell in the center. Also to be noted are the infiltration of leukocytes in the sinusoids and the extremely large Kupffer cells.

In a section from the spleen the tubercles were grouped with numerous leukocytes about them. Many miliary lesions also were present in the lungs. On microscopic section they are seen in the septa and in the alveolar walls. (Fig. 10.) In most instances they are made up of irregular large mononuclear cells and a few lymphocytes, and on occasion multinucleated giant cells are present. In addition, there was an acute bronchopneumonia characterized by poly-

* Photomicrographs were made by the Departments of Illustration, Washington University School of Medicine.

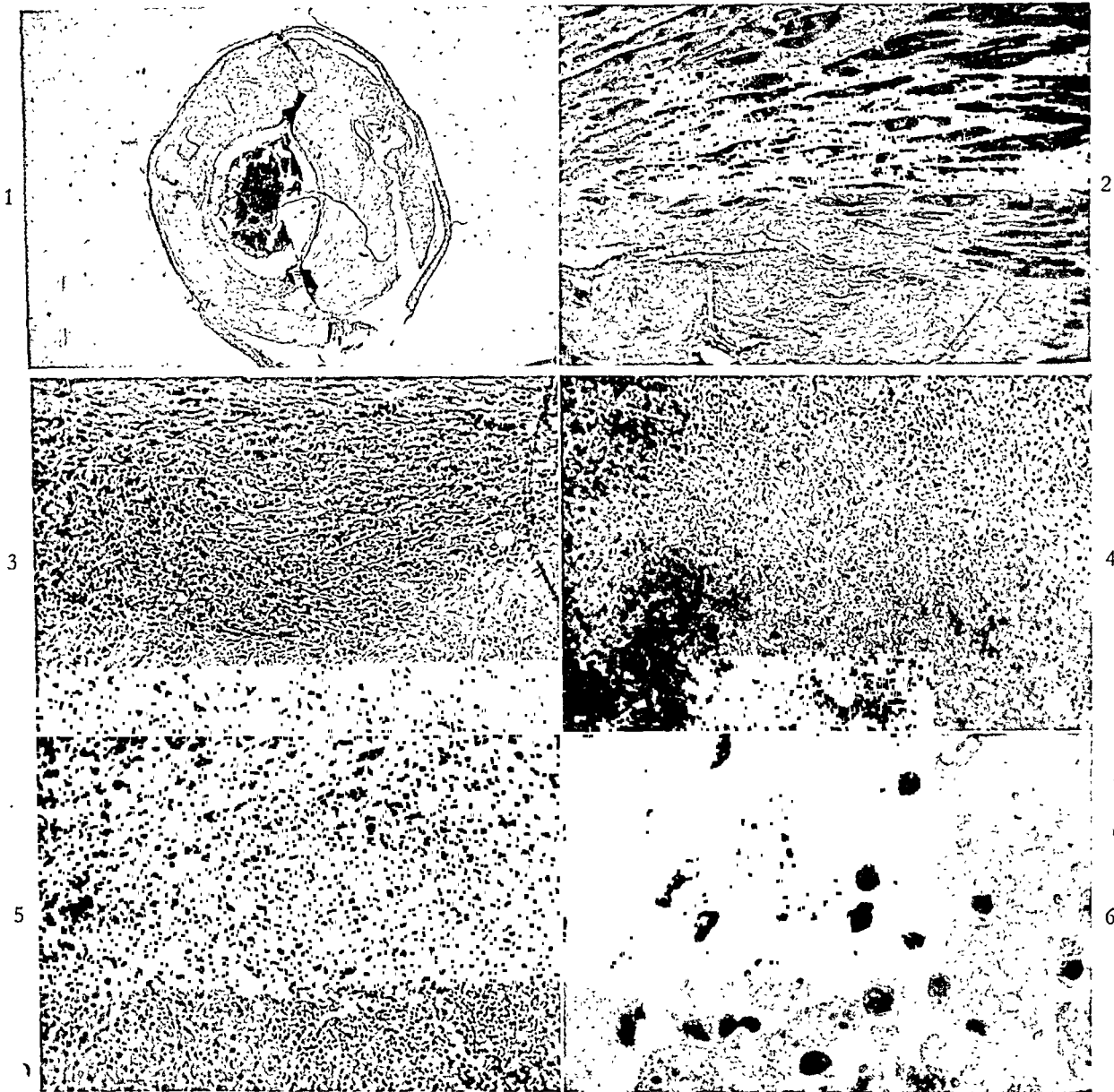


FIG. 1. Section of the descending branch of the left coronary artery showing marked arteriosclerosis and narrowing of the lumen.

FIG. 2. Section of the myocardium in an area of old infarction.

FIG. 3. Section from the left adrenal showing a large caseous area which extends to the capsule. There is cellular infiltration chiefly by lymphocytes.

FIG. 4. Section of the right adrenal gland showing changes similar to those in the left adrenal. The process is less advanced.

FIG. 5. Section from the adrenal showing granulomatous lesions.

FIG. 6. Higher power view of the area seen in Figure 5. The large mononuclear cells contain *Histoplasma capsulatum*.

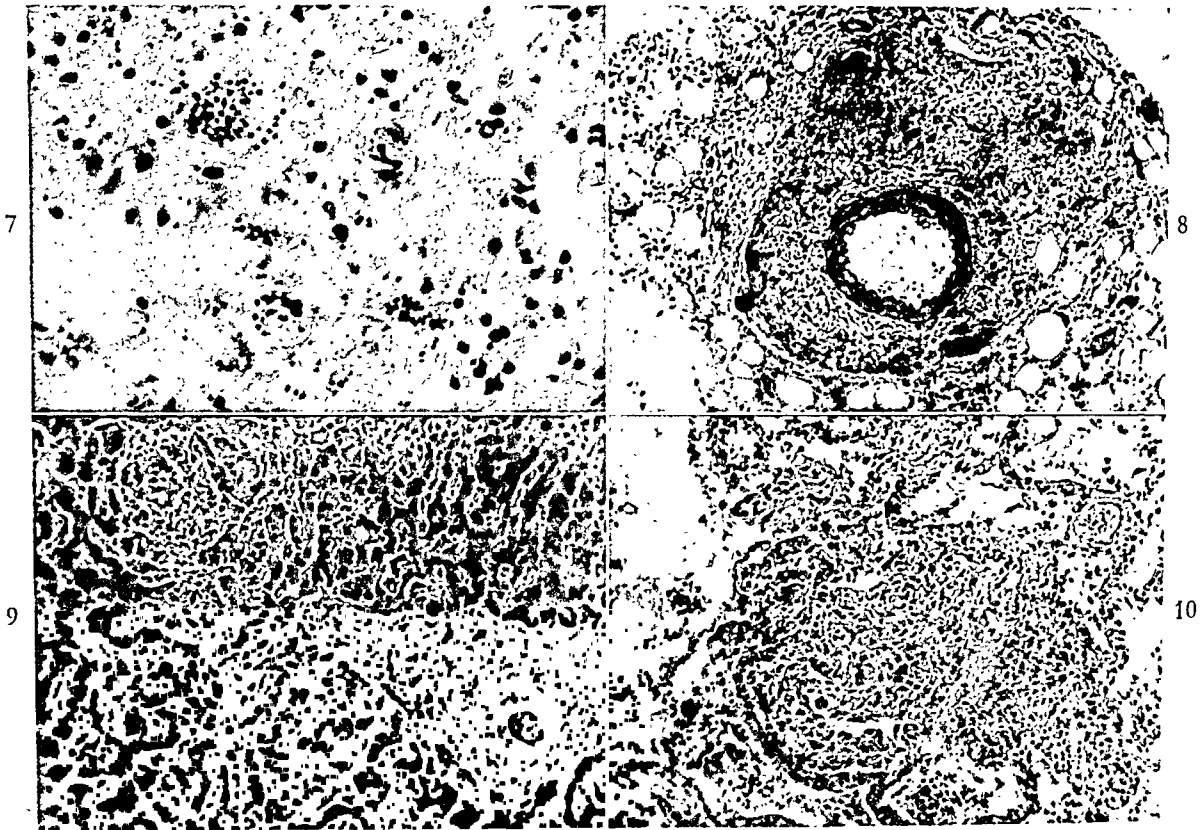


FIG. 7. View through the same area of Fig. 5 to indicate the large number of organisms present.

FIG. 8. Section from the adrenal showing a proliferative type of lesion with miliary granulomas resembling tubercles.

FIG. 9. Section from the liver showing numerous granulomatous lesions. Note the infiltration of leukocytes in the sinusoids and the extremely large Kupffer cells.

FIG. 10. Section from the lung showing granulomatous lesions in the septa and in the alveolar wall.

morphonuclear infiltration and fibrin. A few granulomatous lesions were present in the interstitial tissue of the kidney. (Fig. 11.)



FIG. 11. Similar lesions in the interstitial tissue of the kidney.

There was no generalized lymph node enlargement; however, several broncho-

pulmonary nodes were sectioned and a few granulomatous lesions were found near the capsule. A great deal of anthracosis was present and the reaction was believed to be due principally to anthracosilicosis.

In the study of sections from organs other than the adrenals, *Histoplasma capsulatum* could not be identified with certainty although in a number of the lesions a single body, resembling the organism, was seen. It is believed, however, that all the granulomatous lesions were caused by the same disease process.

As far as the duration of the illness is concerned, the lesion in the left adrenal was much older than that in the right. The lesions in the other organs are of approximately the same age as those in the right

adrenal. The oldest are compatible with a year's duration. An infarct in the adrenal gland probably occurred within five or six months of death and may explain the onset of the clinical manifestations of the disease.

DR. ALEXANDER: Dr. Bottom, is there much calcification visible in the chest film?

DR. BOTTOM: It is seen only in one small area.

DR. ALEXANDER: Is not the incidence of pulmonary calcification high in association with positive skin tests with histoplasmin?

DR. SMITH: Yes.

DR. VIRGIL C. SCOTT: Dr. Smith, how many cases of histoplasmosis have you seen at autopsy?

DR. SMITH: Our first case was seen in 1938 in an adult with histoplasmotric endocarditis.* We have also seen two cases in children. Since 1936, however, there have been about twelve cases reported in this

section of Missouri and the adjacent portions of Illinois.

Pathologic Diagnosis: Fibrocaseous histoplasmosis of the adrenals; miliary granuloma of the liver, spleen, kidney, lung, bronchopulmonary lymph node, bone marrow and pancreas; bronchopneumonia of the upper and lower lobes of the right and the lower lobe of the left lung; arteriosclerosis of the coronary arteries, advanced, with narrowing of the anterior descending and left circumflex branches; healed infarcts of the posterior and anterior wall of the left ventricle, and the anterior part of the interventricular septum; arteriolar nephrosclerosis, moderate; ascites (1,200 cc.); hyalinization of the islands of Langerhans (history of uncontrolled diabetes); arteriosclerosis of the aorta, advanced with ulceration; of the splenic and superior mesenteric arteries, moderate; of the renal, hepatic, inferior mesenteric and pulmonary arteries, slight; anthracosilicotic nodules in the middle and lower lobes of the right lung and bronchopulmonary node.

* BEAMER, P. R., REINHARD, E. H. and GOODOF, I. I. Vegetative endocarditis caused by higher bacteria and fungi. *Am. Heart J.*, 29: 99, 1945.

The Electrocardiographic Diagnosis of Acute Myocardial Infarction in the Presence of the Wolff-Parkinson-White Syndrome*

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THE syndrome of the short PR interval with prolonged QRS complex is apparently a benign congenital anomaly which was first described in 1930 by Wolff, Parkinson, and White.¹ The essential criteria which have been established² as diagnostic of this electrocardiographic abnormality, all of which must be present, include a PR interval of 0.10 second or less, a QRS complex of 0.10 second or more, and slurring of the initial ventricular deflection. In addition, reversal of the above picture to normal is commonly observed either spontaneously, after exercise, or after the administration of certain drugs (atropine, quinidine^{3,4,5}); and paroxysmal tachycardias, either supraventricular or ventricular, frequently occur. Furthermore, this syndrome has been most frequently observed in healthy young males without evidence of organic heart disease.

From its recognition in 1930 to about 1940, investigations of this syndrome were focussed on determining its mechanism, and appear to have established satisfactorily its origin in a structural anomaly which provides an alternative route for conduction of impulses from the sinus node to the ventricles.^{6,7,8} Since 1940, increasing emphasis has been placed on the coexistence of this physiologic peculiarity and various forms of

organic heart disease. At present there are few reports on its association with acute myocardial infarction, a situation of special interest because the diagnosis of the latter is rendered difficult by the basic electrocardiographic changes of this syndrome. We have found reports of only two cases in which the possible coexistence of acute myocardial infarction and the Wolff-Parkinson-White syndrome is considered.^{9,10} We are, therefore, presenting an additional case in which the likelihood of this association was important, and which illustrates the difficulties in the differential diagnosis of acute myocardial infarction by means of the electrocardiogram under these circumstances. The usefulness of the electrocardiogram in the diagnosis of acute myocardial infarction is almost wholly vitiated by the presence of the Wolff-Parkinson-White syndrome.

CASE REPORT

The data submitted below are drawn from records of three hospital admissions, visits to the cardiac clinic, and reports from Dr. Sidney H. Schechner.

The patient, N. S., a fifty-four-year old white male, was first admitted to Beth Israel Hospital on January 2, 1943, because of substernal oppression of four hours' duration. This symptom

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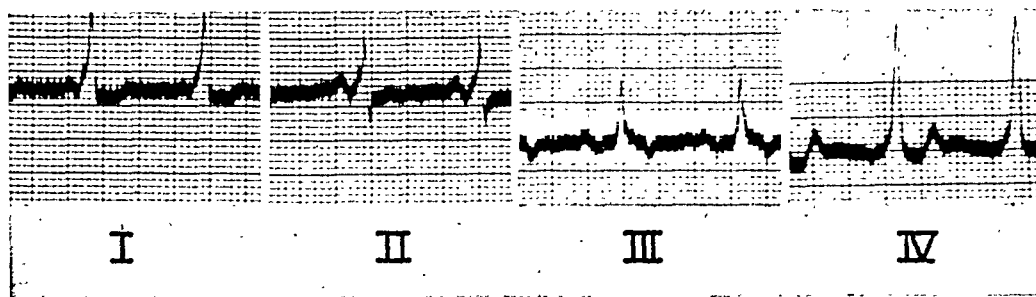


FIG. 1. Tracing taken on April 24, 1941, showing a short P-R interval and prolonged QRS complex with slurring of R_1 and R_2 (four standard leads).

was associated with profuse sweating, dyspnea, several episodes of vomiting, and an ashen grey appearance of the face. Two doses of morphine sulfate, 0.015 Gm., subcutaneously ten minutes apart had been given by his physician. Five years previously a similar episode of tachycardia and chest pain had been relieved by a subcutaneous injection of morphine sulfate, 0.015 Gm. Ever since the first attack, the patient had complained of substernal pain on walking a few blocks, which was promptly relieved by rest. The earliest available electrocardiogram (Fig. 1) taken on April 24, 1941, was characteristic of the Wolff-Parkinson-White syndrome.

On admission the patient appeared acutely ill. The temperature was 99°F. and the respiratory rate was 26 per minute, with moderate dyspnea. The skin was cool and the facies ashen grey. The lungs were clear. The heart was not enlarged. The heart sounds were of poor quality. The rhythm was irregular. The ventricular and pulse rates were 144 per minute. There was no enlargement of the liver or spleen, nor any peripheral edema.

The pertinent findings in the subsequent course are shown in Fig. 2. It may be seen that the temperature rose to 100.2°F. on the first day of illness, then fell to normal where it remained for the rest of the hospital stay. The rhythm became regular and the pulse rate dropped to 84 per minute on the first hospital day. The blood pressure, which was 114/70 on admission, dropped gradually to 80/50 on the fourth hospital day and then recovered so that at the time of discharge it was 115/70. The white blood cell count on admission was 14,000 per cu. mm. with 84 per cent polymorphonuclear leucocytes; the blood sedimentation rate was 1 mm. at the

end of one hour. Subsequent blood counts on the sixth and eleventh hospital days revealed 8,900 leucocytes per cu. mm. with 71 per cent neutrophils, and 7,000 leucocytes per cu. mm. with 77 per cent neutrophils, respectively. A blood sedimentation rate on the ninth hospital day was 3 mm. at the end of one hour. Electrocardiograms taken on the second, eleventh, and thirty-first hospital days showed a short PR interval with prolonged QRS complex with serial changes in the T waves, namely, inversion of T_2 and T_3 . (Fig. 3.) The second tracing, which is not illustrated, showed changes similar to those seen in the third electrocardiogram. (Fig. 3B.)

The hospital course was uneventful. Because of the rise in temperature, leucocytosis, fall in blood pressure and serial changes in the electrocardiogram, a diagnosis of arteriosclerotic heart disease with acute myocardial infarction was made. The patient was discharged to his home on February 14, 1943.

The patient was well until June 8, 1944, when following excitement he experienced a persistent stabbing pain under the left nipple. He was given a hypodermic injection of morphine sulfate, 0.015 Gm., with ensuing marked relief of pain. He was admitted to Beth Israel Hospital two hours after the onset.

At this time, the patient appeared moderately ill. The temperature was 99°F. There was cyanosis of the lips and orthopnea. The neck veins were slightly distended in the upright position. There were occasional moist râles at the base of the right lung. The heart was not enlarged. The heart sounds were of poor quality and tic-tac in nature. The blood pressure was 114/82. The ventricular rate was 230 per minute and the

pulse rate 180 per minute. The rhythm was irregular. The electrocardiogram at this time showed rapid auricular fibrillation with ventricular premature contractions. (Fig. 4A.) The white blood count was 11,300 with 77 per cent neutrophils on the second day of the illness. A

thirteenth day of illness was 5 mm. at the end of an hour.

The patient received quinidine sulfate, 0.6 Gm., daily for the first ten hospital days. The patient was discharged to his home on June 30, 1944.

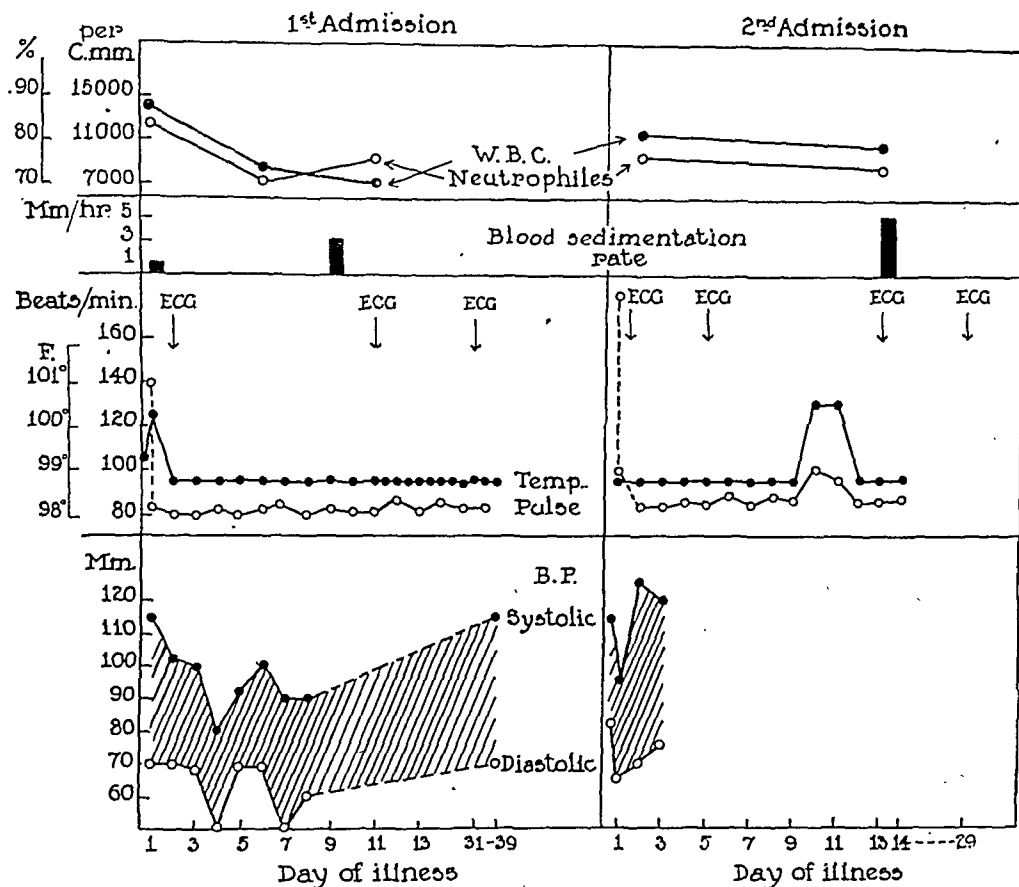


FIG. 2. Chart showing clinical data obtained during the first and second hospital admissions.

second blood count on the thirteenth hospital day showed 10,600 with 73 per cent neutrophils.

The patient was afebrile throughout the hospital course except for an unexplained rise of temperature to 100.4°F. on the tenth and eleventh hospital days. The blood pressure fell to 96/66 with a regular rhythm and ventricular and pulse rates of 100 per minute several hours after admission. On the second day, the blood pressure rose to 126/70 with pulse and ventricular rates of 84 per minute. Subsequent electrocardiograms (Fig. 4B) revealed the syndrome of short PR interval with transient changes in the T waves similar to those seen during the first admission. The blood sedimentation rate on the

The third admission on July 8, 1946, was primarily for the purpose of trying to convert the abnormal rhythm to a normal sinus rhythm by means of atropine or quinidine. On July 9, 1946, a dose of 0.002 Gm. of atropine sulfate was given subcutaneously. Five minutes after its administration, a middle nodal tachycardia with normal QRS complex was present. (Fig. 5B.) Ten minutes after administration of the atropine, the short PR interval with wide QRS complex had reappeared. (Fig. 5C.)

During this admission, the patient was given and has been receiving to date a daily dose of 3 Gm. of quinidine sulfate orally. This amount proved insufficient to cause a reversion of the

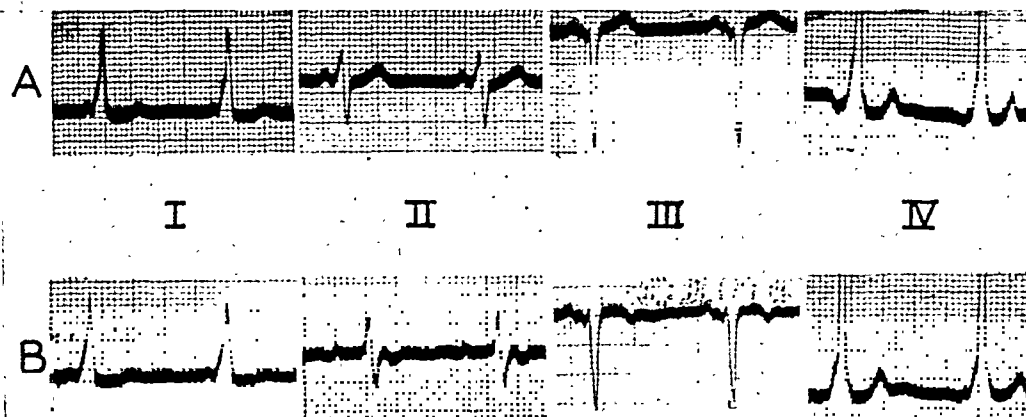


FIG. 3. Tracings taken during the first admission showing serial changes in the T waves. A, third day of illness. All the T waves are upright; B, thirty-first day of illness. T_2 and T_3 are now inverted.

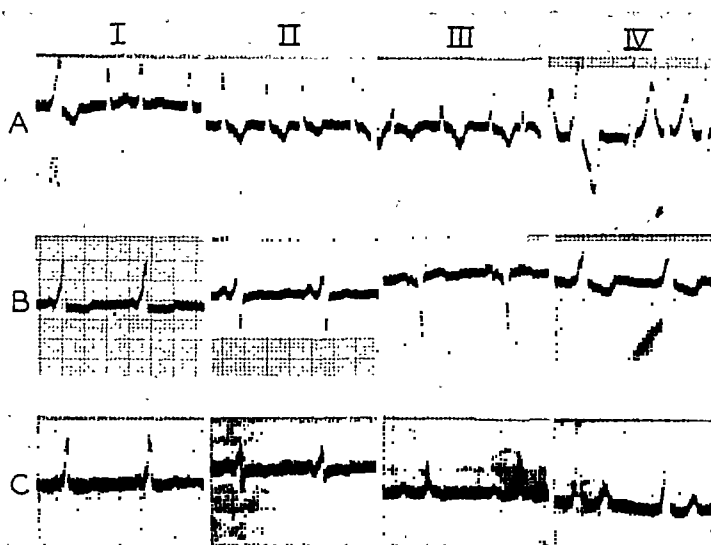


FIG. 4. Tracings taken during the second hospital admission showing a rapid paroxysmal rhythm followed by transient variations in the contour of the T waves. A, first day of illness. Auricular fibrillation (ventricular rate 150 per minute) with ventricular extrasystoles. Note the normal QRS complex time; B, fifth day of illness. T_1 and T_2 are diphasic. T_3 is upright, T_4 is inverted; C, thirteenth day of illness. T_1 is still diphasic, T_2 and T_3 are now inverted and T_4 is upright.

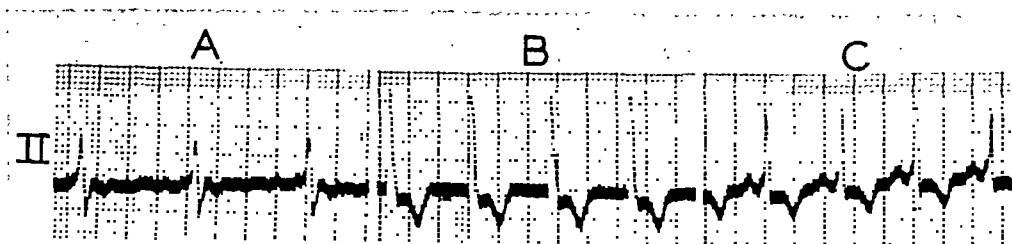


FIG. 5. Influence on the rhythm of atropine sulfate, 0.002 Gm., subcutaneously (lead II only). A, control; B, five minutes after atropine showing a nodal rhythm; C, ten minutes after atropine showing return to the Wolff-Parkinson-White syndrome.

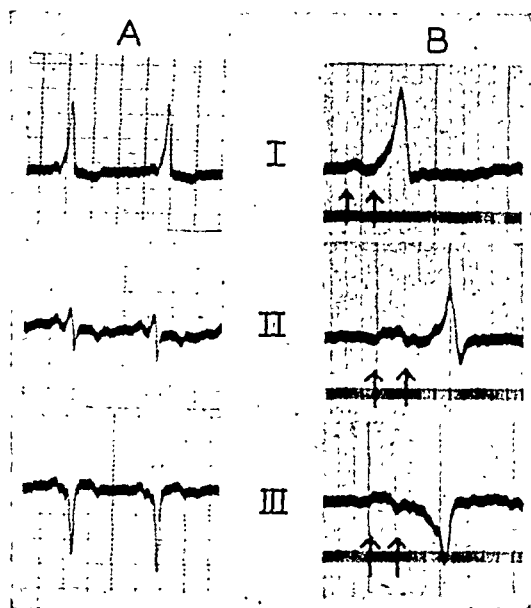


FIG. 6. Comparison of slow (25 mm. per second) and fast (75 mm. per second) moving film (three standard leads) to demonstrate easier recognition of the Wolff-Parkinson-White syndrome. The arrows indicate the P-R interval which measures 0.08 to 0.09 seconds in all leads. A, slow film; B, fast film.

rhythm to normal, although it has prevented a recurrence of any rapid paroxysmal rhythm. All of the tracings since his discharge on July 20, 1946, have shown the Wolff-Parkinson-White syndrome.

COMMENT

In this case it is interesting that the diagnosis both of the Wolff-Parkinson-White syndrome and of acute myocardial infarction was questioned.

Diagnosis of Wolff-Parkinson-White Syndrome. We encountered the argument that the electrocardiogram in this case did not fulfill the essential diagnostic criteria which we have outlined above, because the PR interval in Lead III (Figs. 1 and 6A) appeared to be as long as 0.16 seconds. However, when tracings were taken on a rapidly moving film with camera speed of 75 mm. per second (Fig. 6B) the clearer detail revealed that the isoelectric PQ phase in Lead III actually belonged to the QRS complex rather than to the PR interval.

Thus in this lead also, shortening of the PR interval and widening of the QRS time was demonstrable. It is important to emphasize that an apparently normal PR interval with a QRS complex of normal duration in one or two leads does not preclude a diagnosis of the Wolff-Parkinson-White syndrome, provided at least one standard lead conforms to the criteria which we have listed. Thus it would seem that to allocate correctly an initial isoelectric phase of the QRS complex, the PR interval should be measured in that lead in which it is shortest, and the QRS time in that lead in which it is longest.

Diagnosis of Myocardial Infarction. The serial changes in the electrocardiograms of the first hospital admission (Fig. 3) were accepted at that time as proof of a recent myocardial infarct. However, the fact was overlooked that this criterion, which is usually most reliable in the diagnosis of acute myocardial infarction, namely, serial changes in the T waves, fails to apply in the presence of the Wolff-Parkinson-White syndrome because of the spontaneous inversion of the T waves which occurs frequently in these cases in the absence of any other evidence of a myocardial infarct.¹¹

Furthermore, recent studies^{12,13,14} indicate that the cessation of a rapid paroxysmal rhythm in patients without organic heart disease may be followed by an electrocardiographic picture that resembles that of myocardial infarction with persistence of the abnormal T waves for as long as several weeks.¹² It should be noted that in the case we are reporting, the patient was admitted twice to the hospital following a rapid paroxysmal rhythm. (Fig. 4A.)

It is obvious that both the spontaneous changes in the T waves in the Wolff-Parkinson-White syndrome and the occasional persistence of an abnormal electrocardiogram after the cessation of a rapid paroxysmal rhythm vitiate the usefulness

of serial changes in the T waves in the diagnosis of acute myocardial infarction. This conclusion is in harmony with that of Goldbloom and Dumanis¹⁰ who, on the basis of the general clinical picture, made a diagnosis of acute myocardial infarction in a thirty-three year old man with the Wolff-Parkinson-White syndrome. They noted that the serial changes in the electrocardiogram might not be significant because of the well-known "spontaneous variability of contour of the T wave" in this syndrome. Eichert⁹ has also called attention to the fact that the electrocardiographic peculiarities of the Wolff-Parkinson-White syndrome may simulate those of acute myocardial infarction.

In view of the above spontaneous variations in the T wave in the Wolff-Parkinson-White syndrome, we hoped that in the case of our patient some aid in the diagnosis might be secured from the electrocardiogram if a normal sinus rhythm could be restored by atropine or quinidine. Unfortunately, the restoration of a normal rhythm was not accomplished. However, it is interesting that a middle nodal tachycardia was induced by atropine (Fig. 5B), an effect which is compatible with Katz's hypothesis¹⁵ of the origin of the Wolff-Parkinson-White syndrome in a coronary nodal rhythm rather than in an aberrant pathway from the sinus node.

Confirmatory evidence for the diagnosis of a myocardial infarction which results in either right or left bundle branch block may be afforded by a lengthening of the interval from the initial to the intrinsic deflection of the QRS complex on the involved side, as shown in the six standard precordial leads.¹⁶ In the case which we have reported, however, this technic failed to reveal any difference in the above intervals when the precordial leads from the right and left sides of the heart were compared. In Fig. 7 it may be seen that this interval in leads CF I

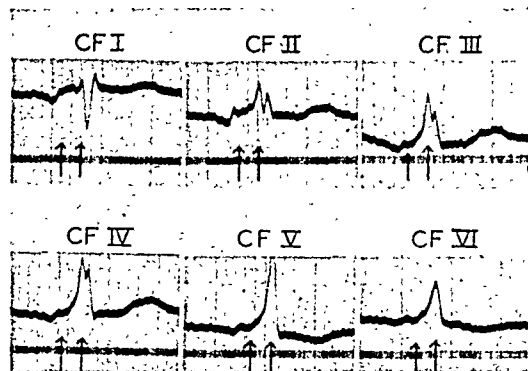


FIG. 7. Precordial leads CF₁ to CF₆. The arrows indicate the interval between the beginning of the QRS complex and the start of the intrinsic deflection (the first rapid downward movement of the string). Absence of organic lesions in the bundles is indicated by the fact that this interval is approximately the same ($0.08 \pm$ seconds) in the leads taken from the right (CF₁ to III) and left (CF_{IV} to VI) sides of the heart.

to CF III (right side) measured 0.07 to 0.08 seconds, and in leads CF IV to CF VI (left side), 0.08 to 0.09 seconds. These findings probably rule out the diagnosis of a bundle branch block on an organic basis. Boyer¹⁶ also studied these measurements in a case of the Wolff-Parkinson-White syndrome and found that the above interval was equal and normal (0.08 seconds) in the precordial leads from the right and left sides of the heart.

In finally evaluating the cardiac diagnosis in this case, we are forced, as we have shown, to discard the electrocardiogram and to rely on the clinical picture and on other laboratory tests. In the first hospital admission, the clinical course presented the classical picture of an acute myocardial infarct, with sudden onset of prolonged substernal oppression with vomiting, collapse symptoms, and a gradual fall of blood pressure to 80/50 on the fourth day of illness. At the onset, fever and leucocytosis were also present. The only laboratory examination which failed to confirm the diagnosis of acute myocardial infarction was the blood sedimentation rate, and it is

well known that an elevation of this value is not essential to the above diagnosis. Therefore, it is quite likely that a fresh myocardial infarction took place just before the first hospital admission. In the second hospital admission, the picture is not so clear-cut, but the symptomatology can be adequately explained by an attack of paroxysmal auricular fibrillation with some degree of left ventricular failure.

SUMMARY AND CONCLUSIONS

1. A case is presented which illustrates the special problems involved in the electrocardiographic diagnosis of acute myocardial infarction in the presence of the syndrome of short PR interval and prolonged QRS complex.

2. The electrocardiographic changes of acute myocardial infarction may be so masked or obscured by the spontaneous variations in the T waves in the Wolff-Parkinson-White syndrome that the electrocardiogram loses its value in the diagnosis of the former condition.

3. Hence, the diagnosis of acute myocardial infarction in the presence of the Wolff-Parkinson-White syndrome can be established only on the basis of criteria other than the electrocardiographic changes.

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ABSTRACTS OF PAPERS PRESENTED AT THE ANNUAL MEETING HELD IN CHICAGO, APRIL 28, 1947

- Electrophoretic Study of Sera from Patients with Pinta and Yaws . . . M. L. DILLON
- Effect of Penicillin on the Transient Bacteremia Following Dental Extraction
ROBERT J. GLASER, ARNOLD DANKNER, SYDNEY B. MATHES AND CARL G. HARFORD
- Rheumatic-like Lesions Found in Unselected Autopsies . . . GEORGE H. REIFENSTEIN
- Fibrinolysin Production by β -Hemolytic Streptococci . . . CHARLES H. RAMMELKAMP
- Endemic Influenza A. E. FELLER
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- Clinical Problem of Pheochromocytoma ELMER C. BARTELS
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- Aqueous Suspensions of Crystalline Estrogenic Substances. A Comparative Assay
ALLAN C. BARNES AND WILLIAM COPE
- Experience with the Thymol Turbidity Test on a General Medical Service
HYMAN B. STILLERMAN
- Enhancement of Plasma Penicillin Concentrations by Caronamide and Sodium Benzoate
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- Criteria for the Diagnosis of Right Ventricular Hypertrophy Using Unipolar Limb and Precordial Leads . . . MAURICE SOKOLOW AND THOMAS P. LYON
- Electrocardiograms with Poor Prognosis in Acute Coronary Occlusion
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- Relative Effectiveness of Various Diuretics in Causing Sodium Excretion in Pregnant Women . . . WILLIS E. BROWN AND J. T. BRADBURY
- Function of the Stomach as Observed in Fistulous Human Subjects, with Special Reference to the Action of Drugs and the Effects of Vagotomy
STEWART WOLF AND HAROLD G. WOLFF

ELECTROPHORETIC STUDY OF SERA FROM PATIENTS WITH PINTA AND YAWS

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(Introduced by GRANT TAYLOR, Ph.D.)

It has been demonstrated by Cooper, Rein and Beard with sera from two patients with kala-azar that the presence of hyperproteinemia, hyperglobulinemia, or hypergammaglobulinemia could not be used to prove or disprove the specificity of positive serological reactions for syphilis. This report extends the above work by a study of sera from three patients with pinta and three patients with yaws. Electrophoretic studies and serodiagnostic tests were performed, protein concentrations were determined and again it was demonstrated that there is no correlation of the serodiagnostic tests with hyperproteinemia, hyperglobulinemia or hypergammaglobulinemia.

EFFECT OF PENICILLIN ON THE TRANSIENT BACTEREMIA FOLLOWING DENTAL EXTRACTION

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MATHES, M.D. *and* CARL G.

HARFORD, M.D.

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This study was undertaken to determine the effect of penicillin on the transient bacteremia known to follow dental extraction. It was considered that such a study would aid in the evaluation of the prophylactic use of penicillin in patients with rheumatic and congenital heart disease who require dental operations.

Blood cultures were taken before and immediately after extraction of one or more teeth in two series of patients, each forty in number. In the first, or control series, alpha-hemolytic streptococci or non-hemolytic streptococci were recovered from over 60 per cent of the post-extraction cultures. In the second series, the patients were given large doses of penicillin

over a twenty-four-hour period prior to extraction. In this group, approximately 40 per cent of the postextraction cultures were positive for alpha-hemolytic streptococci or non-hemolytic streptococci. In the control series the former organism predominated, whereas in the penicillin series the latter organism predominated.

The use of penicillin did not result in a significant decrease in the occurrence of bacteremia after extraction of teeth in patients with normal gums; however, in those with gingivitis or pyorrhea a definite decrease in incidence of positive blood cultures was noted. Indeed, the over-all reduction of positive blood cultures with the use of penicillin was due entirely to a decrease in the incidence of bacteremia following extraction of teeth from patients with gingivitis or pyorrhea.

It was concluded from this investigation that prior to extraction of teeth in patients with rheumatic or congenital heart disease, penicillin should be given for at least twenty-four hours in high dosage to those patients with gingivitis or pyorrhea and should be continued for two or three days after extraction. In patients whose gums are normal penicillin may be begun immediately prior to extraction but should be continued for approximately two to three days. It is postulated that the use of penicillin for two or three days following extraction represents, in effect, the earliest possible treatment of bacterial endocarditis if it becomes established following extraction. Whether this method will prove totally effective awaits further experience.

RHEUMATIC-LIKE LESIONS FOUND IN UNSELECTED AUTOPSIES

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A clinical pathological study was made of hearts from 145 unselected autopsies under conditions favorable to unbiased observations. The results of this study may be summarized as follows:

1. Rheumatic or rheumatic-like microscopic nodules were found in almost 52 per cent of the hearts. These nodules occurred in various parts of the heart, most frequently in the myocardium, atrial endocardium, and annuli and spongiosa

of the mitral and aortic valves. There was no sharp line of differentiation between rheumatic and rheumatic-like nodules.

2. Fifty per cent of the hearts with typical rheumatic nodules were obtained from patients fifty years or more of age and a number of typical rheumatic nodules were observed in those hearts from patients seventy years of age or older.

3. Rheumatic or rheumatic-like nodules were seen most commonly in association with bacterial infections, the presence of bacteremia (not necessarily beta hemolytic streptococcic), clinical rheumatic fever or rheumatic histories.

4. Gross rheumatic or rheumatic-like valvular lesions were observed in 48 per cent of the 145 hearts. The hearts with these gross lesions had more rheumatic or rheumatic-like microscopic changes than the hearts without gross valvular lesions.

5. Based on these observations, it seems logical to assume that a rheumatic-like carditis is more frequent than is generally believed. It is not necessarily restricted to younger age groups; it may be slight, moderate or marked and may lead to deformity or heal with minimal or no deformity. This carditis was found associated most frequently with bacterial infections, especially bacteremias, not necessarily beta-hemolytic streptococcic.

FIBRINOLYSIN PRODUCTION BY β -HEMOLYTIC STREPTOCOCCI

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Although little is known concerning the rôle of streptococcal fibrinolysis in the pathogenesis of disease, there is some indication that β -hemolytic streptococci which produce large amounts of fibrinolysin are usually associated with severe infections, whereas little fibrinolysin is produced by strains from mild infections. In order to investigate this relationship further a technic for measuring the amount of fibrinolysin produced by β -hemolytic streptococci was devised. Many strains of streptococci isolated from the nasopharynx of patients with respira-

tory disease and from normal subjects were studied by this method. Strains of group A streptococci isolated in various parts of the United States were similarly examined.

Analysis of the results of these tests showed that the ability to produce fibrinolysin varied according to the Lancefield group and that in general those groups commonly considered to be pathogenic produce considerable amounts. Group A streptococci appeared to vary in their fibrinolytic capacity according to the Lancefield type of organism. Organisms of one type seemed to exhibit a similar fibrinolytic capacity irrespective of the section of the country from which they were derived. No relationship was apparent between the severity of the disease and the fibrinolytic ability. A correlation was demonstrated between the amount of fibrinolysin produced and the ability of the strain to stimulate antifibrinolysin in the patient.

ENDEMIC INFLUENZA

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Until recently, it had been widely believed that influenza was essentially, if not entirely, an epidemic disease. However, many reports of the occurrence of sporadic cases of influenza A and influenza B have suggested that influenza viruses A and B are in constant circulation in a population and that cases of influenza would be found repeatedly in non-epidemic periods if a search were made. The result of such a continuous search for cases of influenza over a period of nearly three and one-half years at Fort Bragg, N. C., is the subject of the present report.

Respiratory disease admissions to the Station Hospital were the source of cases. Acute and convalescent phase sera were obtained from each patient and tested for antibodies to influenza viruses A and B. The diagnosis of influenza was made when a fourfold or greater increase in titer of antibodies occurred. The study was started November, 1942 and terminated March, 1946. A total of 2,932 respiratory admissions was studied and those patients selected included all types of respiratory disease.

Influenza A and influenza B occurred sporadically as well as in epidemic form. One localized outbreak of influenza B occurred. It was found that cases of influenza occurring in non-epidemic periods were very difficult or impossible to recognize clinically.

The conclusion was reached that influenza may be viewed as an endemic disease which periodically erupts in epidemic form.

STREPTOMYCIN TREATMENT OF TULAREMIA

JOHN B. JOHNSON, M.D., *and (by invitation)*
CHARLES B. WILKINSON, M.D. *and* EDMUNDO
FIGUERAS, M.D.

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This report summarizes the results obtained in five patients with tularemia who were treated with streptomycin. Three of the cases were of the ulceroglandular type and two were of the pulmonic type. The latter and one of the former were critically ill on admission. In two cases the streptomycin was started during the first week of the disease, in two others it was started in the third week and in one, the ninth week of the disease. The daily dose of streptomycin was 0.4 Gm. in two cases and 0.8 Gm. in three cases. The drug was continued until the temperature was normal for several days. In each instance there was a sharp drop in temperature within twenty-four hours after the institution of treatment. The temperature reached and remained normal on the fourth day in one patient, on the twelfth day in three patients and on the eighteenth day in one patient. All patients showed rapid subjective improvement.

Two of the three patients with the ulceroglandular type of tularemia required surgical drainage even though they were given streptomycin into the bubo as well as by intramuscular injection. In these two patients treatment was not started until the third and ninth week of the disease. In the patient whose lymphadenopathy resolved without drainage treatment was started in the first week of the disease.

One patient who had been pregnant for three months and whose disease had gone untreated for nine weeks aborted after three weeks of

streptomycin therapy. Pathological examination of the placenta and fetus showed no changes which could be attributed to streptomycin or tularemia.

One patient, a chronic alcoholic, developed delirium tremens. Treatment had to be resumed in one patient with pneumonic involvement because of a recurrence of fever. This was true even though this patient had received 12.8 Gm. of streptomycin in sixteen days. One patient developed an increase in fever on two occasions while streptomycin was being given; in each instance the temperature fell following penicillin therapy.

Streptomycin was considered very effective therapy in these five cases as determined by the reduction in days of fever, bed ridden days and duration of buboes. In the two cases where streptomycin was started during the first week of the disease, the agglutination titer was 1:40 or less on admission. In each instance a rising titer of agglutinins occurred suggesting that the streptomycin did not interfere with antibody formation.

CLINICAL PROBLEM OF PHEOCHROMOCYTOMA

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A study was made of sympathetic tumors of the adrenal gland and four cases were reported which showed the various clinical manifestations of this disease. Since vasomotor symptoms were prevalent in all these cases, one must consider an adrenal tumor in patients presenting these complaints irrespective of the severity of the symptoms. If the correct diagnosis is made, as in Case I, (and this is now possible with newer diagnostic procedures such as histamine and mecholyl) and if the patient's cardiac reserve is sufficient to tolerate the operation and its hypertensive reaction, a clinical cure results. If the correct diagnosis is not made fixed hypertension with progressive cardiac and renal failure results (Case II). If an adrenal tumor is found, as in Case III, the true nature of the tumor should be determined before operation since the anesthesiologist and surgeon will then be aware of

the problem and better able to plan the anesthesia, avoiding spinal, and at operation proceed with dispatch to remove the tumor. Should an unusual hypertensive reaction be observed by the anesthesiologist during the course of an elective operation, as in Case iv, the diagnosis of sympathetic adrenal tumor should be considered and if proven by abdominal exploration serious consideration should be given to its removal.

The use of epinephrine, in the event of a shock state with pulmonary edema, during the operation for removal of these adrenal tumors is not judicious since actually the state of shock is best explained as the result of left ventricular heart strain secondary to increased peripheral resistance owing to an excess circulatory epinephrine. Therapy of the condition includes rapid removal of the tumor and the administration of oxygen, digitalis and perhaps peripheral vasodilating agents. Recovery from the reaction depends chiefly on the patient's cardiac reserve.

USE OF TETRAETHYLAMMONIUM BROMIDE AS A DIAGNOSTIC TEST FOR PHEOCHROMOCYTOMA

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The pre- and postoperative reactions of a patient with a pheochromocytoma to the intravenous administration of histamine diphosphate and of tetraethylammonium bromide offer a diagnostic test for the presence of epinephrine tumors.

The patient's reactions to intravenous injections of 2 ml. of a saline solution containing 0.025 mg. of histamine phosphate, then of a solution containing 100 mg. of tetraethylammonium bromide and finally of 2 ml. of saline are compared.

Within one minute after the administration of histamine the patient developed a typical attack associated with a rise in blood pressure from 160/105 to 280/160. The reading returned approximately to normal within five minutes. The pulse rate rose from 94 to 116 and then fell to 96. Although the resting blood pressure was

somewhat higher before tetraethylammonium bromide was given, the response was just as pronounced and lasted considerably longer. The reading rose from a basal level of 175/105 to 270/160 in thirty seconds and the elevation lasted fifteen minutes. The pulse rate rose from 75 to 130 and returned to 90. The decrease in the blood pressure when the patient changed from a supine to an erect position was dramatic, the reading falling from 230/125 to 95/80. When the 2 ml. injection of saline was given no detectable change in the blood pressure or pulse rate occurred.

The above tests were repeated approximately two months postoperatively and the patient evinced no reaction whatsoever to the injection of histamine, tetraethylammonium bromide or saline.

According to our observations on this patient the use of tetraethylammonium bromide as a test for pheochromocytoma has one advantage over that of histamine. When tetraethylammonium was employed, dangerously high levels of the blood pressure could be controlled simply by having the patient sit up or stand. This resulted in a prompt fall in blood pressure and a disappearance of the symptoms. Lyons and his co-workers noted this phenomenon in their studies on normal and hypertensive individuals; hence, it would appear that with the use of a tilting bed or table tetraethylammonium bromide could be employed with perfect safety in testing for the presence of a pheochromocytoma.

PEPTIC ULCER THERAPY—THE USE OF SYNTHETIC RESINS

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In 1945 Segal, Hodge, Watson and Scott reported on the use of a polyamine formaldehyde resin in removing hydrochloric acid from solution. One concludes from this article, that although effective, such large amounts of resin would be needed to inactivate the acid in the stomach that the use of resins in clinical medicine would not be practical. The next year, Martin and Wilkinson found that by using a more finely sieved resin, clinical application might prove practical. "One Gm. of their resin,

Amberlite IR 4* took 250 ml. of 0.1 N HCL to pH 4.

We have made neutralization experiments on the freshly extracted gastric juice of one hundred patients. The free acid in these specimens varied from 6 to 69 clinical degrees and in amounts from 15 to 100 ml. Some of the experiments were performed at room temperature and others at 99°F. Toepfer's reagent was used as an indicator. Resin was added with constant stirring. It was found that neutralization took as long as forty-five minutes. Approximately 50 ml. of gastric juice of 25 degrees of acidity was neutralized by 0.1 Gm. of resin. The viscosity of the juice appears to be a factor in determining the number of resin particles exposed to acid.

We have used resin as an antacid in treating forty-seven patients with peptic ulcer in doses of 0.5 to 1 Gm., four to six times a day. We have found it clinically as satisfactory as magnesium trisilicate or aluminum hydroxide and phosphate suspensions. We used it first in powder form but because of its phenolic odor and sandy feeling we found its prescription in capsule form more practical. It appears to have the following advantages over commonly used metallic salt antacids: (1) It has no effect on the acid base balance of the body; (2) it does not alkalinize the urinary tract; (3) it causes neither diarrhea nor constipation; (4) it causes no perianal burning and (5) to date we have noted no toxic or allergic reactions.

PHARMACOLOGICAL PROMOTION OF EVACUATION FROM THE POST- VAGOTOMY STOMACH

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One of the complications that has developed following section of the vagus nerves for peptic ulcer is gastric retention. This occurs especially in those patients who have not had a gastroenterostomy or who do not have an adequately functioning stoma. For relief of the retention some type of a gastroenterostomy has sometimes been required. Such surgical interference, how-

* Resinat.

ever, has been avoided in six of our postvagotomy patients who had gastric retention by the use of the parasympathomimetic drug, urethane of β -methyl choline (urecholine).

The drug has been administered orally with each of the main meals of the day in those patients who do not have complete retention. When nothing passes into the intestine the drug must be given subcutaneously. Sublingual or gastric absorption of the drug has not been demonstrated. The usual dose is 5 to 10 mg., but this must be determined for the individual case.

The patients remained free of symptoms of retention while taking the drug but have not done so when a "placebo" was substituted or when the drug was discontinued.

Within five to ten minutes after the subcutaneous injection of a 5 to 10 mg. dose of urecholine, peristaltic activity can be demonstrated roentgenologically or by means of a recording balloon. The period of induced activity lasts forty to sixty minutes and can be reproduced by a second injection. It does not give rise to a significant increase in free hydrochloric acid in the gastric juice when the patient is permitted to swallow saliva or when the stomach contains neutralizing food substances. No untoward side-effects have been noted or complained of when it is administered orally. Following the subcutaneous injection of a 10 mg. dose, flushing, sweating and salivation may occur; sometimes abdominal cramps and a desire to evacuate the urinary bladder also occurs. These phenomena are not so severe as those that follow a comparable dose of mecholyl. The effects of urecholine can be neutralized at any time by an injection of atropine, more promptly when it is given intravenously.

EFFECT OF ATROPINE ON THE CEPHALIC AND GASTRIC PHASES OF GASTRIC ACTIVITY

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The influence of atropine on the cephalic and gastric phases of gastric activity has never been

clearly established. Because of the recent introduction of bilateral vagotomy in the treatment of peptic ulceration the effect of atropine on the vagus nerve has become of greater interest in evaluating the importance of these two phases of gastric activity. Adult patients were investigated in this study. Our primary interest was in those with duodenal or gastric ulcers but normal adults were also studied. Gastric motility and secretory activity were studied in the fasting post absorptive period for a continuous period of three to six hours by means of a double lumen tube which was inserted into the stomach. A rubber balloon was attached to the distal tube which was then placed in the antrum. The balloon was inflated with 10 ml. of air and the antral motility recorded on a smoked kymograph through a water manometer. The proximal tube was used for continuous aspiration of gastric contents. All gastric contents passed through a glass electrode attached to a Beckman pH meter so that pH readings could be made at frequent (usually fifteen minute) intervals. Gastric contents were measured for volume, titrated for free and total acidity and analyzed for peptic activity, non-protein nitrogen and protein nitrogen. Atropine was administered subcutaneously and intravenously in doses varying from 0.4 to 1.2 mg. There was some variation in individual cases but generally 0.8 mg. of atropine or more by either route of administration caused a marked decrease in tone and peristaltic type of gastric motility. The volume of gastric secretion was markedly decreased.

The free acidity was generally decreased but there was some variability in this effect. Spontaneous motility and secretory volume could be increased by application of noxious emotional stimuli to the subject. There was a concomitant increase in pulse rate and blood pressure. After atropinization noxious stimuli had no augmenting influence on motility or secretion but other somatic functions responded as indicated by rise in blood pressure and increase in pulse rate. Atropine abolished the increased motor and secretory activity induced by insulin hypoglycemia and had a similar effect in a single case of hypoglycemia. Atropine given after the administration of liver extract by the stomach

tube decreased the motor activity of the stomach but had little or no influence on secretory activity.

AQUEOUS SUSPENSIONS OF CRYSTALLINE ESTROGENIC SUBSTANCES. A COMPARATIVE ASSAY

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Since the introduction by Freed and Greenhill of aqueous suspensions of crystalline estrogens this form of therapy has received increasing attention. In comparison with pellet implantation, injections of such suspensions are simpler and introduce the material in more finely divided form. In contrast with oil and wax solutions there is no sensitivity to the vehicle and no formation of encapsulated collections of foreign matter.

To date the reported assays of crystalline estrogens in aqueous suspension have been based on the subjective response of menopausal women and the original comparison was with a crystalline suspension—not solution—in oil. The present study was undertaken to provide more objective evidence by a comparative assay in humans of equivalent therapeutic products.

The preparations under study were administered to a group of post-menopausal women and the response of the vaginal epithelium was followed by vaginal smears. These were stained by the Shorr technic and were classified in three groups: 1. Atrophic. There was complete or almost complete absence of estrogenic stimulation. The smear had a high white count, small cells and vesicular nuclei. The stain was predominantly blue; 2. intermediate. There was some estrogenic stimulation with few white cells, pyknotic as well as vesicular nuclei and the stain was predominantly green. 3. advanced. There was full stimulation with large, flat cells with pyknotic nuclei. The stain was predominantly red.

A suspension of estrogenic substance in water was compared by this method with a solution of estrogenic substance in oil and with solutions of alpha-estradiol in oil. The highest levels were

invariable reached with the aqueous suspension and were usually found on the fifth or sixth day.

The duration of effect of the aqueous suspension was greater than a comparable amount of estrogenic substance in oil, as well as a comparable unitage of the estradiol. Doubling the dose of either form of medication had a tendency to double the effective time without necessarily raising the peak level of reaction. The response to a 2 mg. dose of any of the drugs under consideration was limited to two weeks. There was no evidence of a prolonged action (up to ten weeks) reported on the basis of subjective response.

EXPERIENCE WITH THE THYMOL TURBIDITY TEST ON A GENERAL MEDICAL SERVICE

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(Introduced by BRUCE LOGUE, M.D.)

The thymol turbidity test was performed on the sera of approximately 500 patients from an active medical service. Many of these patients were followed serially during and after their hospital stay. The cases included a number of patients in whom liver dysfunction was not suspected.

The thymol turbidity test was found to be an excellent index of liver function in cases of infectious hepatitis and cirrhosis. The results confirmed previous work done with these diseases. The test is of great value in following the progress of cases of infectious hepatitis.

A series of twenty-one proven cases of lymphogranuloma venereum was studied and twenty of them were found to have positive thymol turbidity tests. In view of this the positive thymol turbidity test must be treated with caution in negro patients. The test was also frequently positive in patients with rheumatoid arthritis, congestive failure and strongly positive in such generalized diseases as disseminated lupus erythematosus, dermatomyositis and scleroderma.

The thymol turbidity test was compared to the cephalin flocculation test and it was found that both tests were positive in 35 per cent of the cases, both negative in 37 per cent; thymol turbidity positive and cephalin flocculation

negative in 22 per cent while the thymol turbidity was negative and the cephalin flocculation positive in 6 per cent of the cases.

ENHANCEMENT OF PLASMA PENICILLIN CONCENTRATIONS BY CARONAMIDE AND SODIUM BENZOATE

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Caronamide (4- carboxy phenylmethane sulfonamide) has been found to decrease the renal excretion of penicillin. In clinical trials the oral administration of caronamide increased plasma penicillin concentrations when penicillin was administered intramuscularly as well as orally.

In the present study the effect of caronamide on plasma penicillin concentrations was determined in approximately fifty normal adults. Penicillin was administered by various routes during the day and plasma concentrations determined. On a succeeding day the same subjects received penicillin on the same dosage schedule and in addition, took caronamide by mouth, usually in a dosage of 2 Gm. every two hours. No evidences of toxicity clearly attributable to caronamide were encountered.

The administration of 100,000 units of penicillin by mouth every two hours resulted in low plasma concentrations one and two hours after each dose. The concurrent administration of caronamide resulted in a two to sixteen-fold increase in plasma penicillin concentrations in a great majority of instances.

In subjects who received 25,000 and 50,000 units of penicillin intramuscularly the concurrent administration of caronamide likewise resulted in a two to eight-fold increase in plasma penicillin concentrations in most instances. The effect of caronamide in a fixed dosage was more marked with smaller than with larger doses of penicillin. Some data on the rapidity and duration of the action of caronamide were obtained.

When penicillin was administered in beeswax and peanut oil the effects of caronamide were variable but in the majority of instances plasma penicillin concentrations were increased.

Caronamide had no effect on the plasma concentration of streptomycin when the latter

was administered in multiple intramuscular injections.

Sodium benzoate, in general, was as effective as caronamide in increasing plasma penicillin concentrations when penicillin was administered by mouth or intramuscularly. The administration of both sodium benzoate and caronamide to subjects receiving penicillin by mouth resulted in a greater increase in plasma penicillin concentrations than was affected by either of these agents alone.

A STUDY OF THE ANALGESIC AND TOXIC PROPERTIES OF DOLOPHINE (6-DIMETHYL-AMINO-4, 4-DIPHENYL 3-HEPTANONE HYDROCHLORIDE). A PRELIMINARY REPORT

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A study of the analgesic and toxic properties of 6-dimethyl-amino-4, 4 diphenyl 3-heptanone hydrochloride, also known as dolophine or #10820, has been made in ninety-four patients.

Pain in the majority of these patients was due to advanced malignant disease. In the remainder of the group the effect of this drug on the pain associated with dysmenorrhea, osteomyelitis, rheumatoid arthritis, peptic ulcer and panophthalmitis was studied. A small group was studied for suppression of cough and in a series of five patients the drug was used for pre- and postoperative analgesia.

Ages of the patients studied ranged from fourteen to eighty-eight years; the largest number of patients were from forty-five to sixty-five years of age. Oral and subcutaneous routes of administration were used. According to the degree of pain single subcutaneous dosages were varied from 2.5 mg. to 17.5 mg. The single oral dose varied from 2.5 mg. to a maximum of 10 mg. A total of approximately 10,000 injections and approximately 500 oral doses have been given.

Analgesia was obtained in seventy-two patients to whom the drug was given subcutaneously and it was maintained at satisfactory levels

in all but a small group. Duration of pain relief varied from two to eight hours; in most patients relief was sustained for four hours. In twenty-one patients who were given the drug orally the most satisfactory results were obtained in cough suppression.

Toxic reactions occurred in only five of the seventy-two patients given the drug subcutaneously. These reactions were a slight lethargy in two, apprehension and paresthesias in one, severe delirium in one and transitory hallucinations in another. Toxic manifestations were common in the patients who received the drug by mouth. Of twenty-one patients, sixteen had one or more of the following reactions: anorexia, nausea, vomiting, diarrhea, dizziness, weakness or diaphoresis.

These early clinical experiences indicate that dolophine is a powerful analgesic agent which may be used subcutaneously with a minimum of toxic reactions. Insufficient data is available to determine the tolerance and habituation factors.

The work was supported by a grant from the Eli Lilly Company, Indianapolis, Ind.

PHARMACOLOGY AND THE CLINICAL USE OF DOLOPHINE (6-DIMETHYL-AMINO-4, 4-DIPHENYL 3-HEPTANONE HYDROCHLORIDE)

K. G. KOHLSTAEDT, M.D. (*by invitation*)
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The analgesic effects of dolophine have been studied—men and animals serving as test subjects. In rats the intraperitoneal injection of 1 to 2 mg. per Kg. produced analgesia as measured by the tail-pinching method of Haffner. Using the Hardy, Wolff, Goodell thermal technic, dolophine (5 mg. per Kg.) was administered subcutaneously to dogs and was found to be more potent than the same amount of morphine. Five mg. raised the pain threshold in man.

More than 300 patients have received dolophine for the relief of pain (2.5 to 15 mg. subcutaneously or orally). Analgesia was main-

tained at a satisfactory level in 79 per cent of these individuals. On the general and gynecological surgery wards postoperative pain and discomfort were completely controlled in sixty-four out of seventy-nine patients. The administration of dolophine at regular intervals alleviated severe, chronic pain for a period of six months in ten patients.

This heptanone derivative in doses of 1.5 to 2.0 mg. (by mouth) was found to suppress the cough reflex. It has been used for this purpose in patients with bronchiectasis, pertussis, bronchiogenic carcinoma and chronic passive pulmonary congestion due to cardiac failure. In forty-eight patients with advanced pulmonary tuberculosis, pleuritic pain and cough were controlled as well or better with dolophine than with codeine. The effect of therapeutic doses of dolophine on respiration, the electrocardiogram, rectal temperature, arterial pressure and hepatic function has been observed. This compound occasionally caused unpleasant side reaction, e.g., nausea, vomiting, light-headedness, diaphoresis and mental confusion. These untoward manifestations occurred following both oral and parenteral administration and were most frequent in ambulatory patients with mild pain.

Analgesic doses of this drug produced less sedation and narcosis than therapeutically equivalent amounts of morphine. The results of clinical studies indicate that dolophine is a potent analgesic and that it may be used to alleviate many types of pain.

CLINICAL OBSERVATIONS IN PATIENTS TREATED WITH ANTIRETICULAR CYTOTOXIC SERUM. PRELIMINARY REPORT

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Within the past eighteen months 106 patients have been treated with antireticular cytotoxic serum in the Ochsner Clinic. Material was prepared by Dr. Harry Goldblatt according to the method of Marchuk and was usually administered subcutaneously in dosages of 0.5 ml. of 1

to 10 dilution on the first day, 1.0 ml. on the fourth day and 1.5 ml. on the seventh day; courses were generally repeated every six weeks.

The series here reported consists of sixty-two cases of far advanced cancer and thirty-eight cases of other diseases. Of the sixty-two patients with cancer, forty-nine are dead and thirteen living, the longest length of life being thirteen months from the first injection of serum. Although it cannot be said that any lives were prolonged by this serum treatment, ten patients experienced a marked relief of pain, a gain in weight, an increased appetite, a sense of well-being and eleven noted moderate benefit.

The second group of thirty-eight cases includes twenty-one cases of rheumatoid arthritis; three of degenerative arthritis; two each of osteoporosis, Hodgkin's disease and acute monocytic leukemia; single cases of myeloid leukemia, gouty arthritis, lupus erythematosus disseminatus, radiation neuritis, dermatomyositis, multiple myeloma, senile emphysema and epidural abscess. Pronounced relief was obtained by twelve patients with rheumatoid arthritis and moderate relief by one. The patient with myeloid leukemia responded dramatically to repeated injections. The patients with osteoporosis had complete relief of pain and those with Hodgkin's disease, multiple myeloma and lupus erythematosus disseminatus have obtained moderate benefit; the others have not been helped at all. Both patients with acute monocytic leukemia and the one with multiple myeloma are now dead.

Reactions occurred in twelve patients, nine of whom were in the non-cancerous group. These usually consisted of indurated, reddened, painful areas of varying extent in the injected arm, plus a fever of about 101°F. However, rash, arthralgia and bleb formation occurred in a few instances.

Particularly interesting cases, reported in detail, include: (1) a patient with carcinoma of the cervix in whom symptoms have completely disappeared following five courses of injections; (2) the patient with myeloid leukemia whose peripheral blood made repeated responses to the course of serum and (3) cases of rheumatoid arthritis and osteoporosis in which dramatic relief of pain has been noted.

INTRAVENOUS USE OF SODIUM AMYTAL IN PSYCHOSOMATIC DISORDERS

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The action of intravenously administered sodium amytal in 500 patients in military and civilian practice has been analyzed from the standpoints of its usefulness in diagnosis, treatment, prognosis and investigation of the etiology of bodily disorders arising from problems of personality adjustment.

The drug has been found useful, chiefly as follows:

1. Diagnostically in distinguishing between irreversible, structurally determined disorders and functional disorders of organ systems.
2. Diagnostically in distinguishing between neurosis and malingering.
3. Diagnostically in the elucidation of dynamically significant situational conflicts.
4. Therapeutically in the alleviation of troublesome symptoms.
5. Therapeutically when data obtained during sodium amytal interview are used in formulation to the patient, when the reassuring value of the reversibility of symptoms is used or in the use of hypnotic or posthypnotic suggestions.
6. Prognostically in determining the depth of the disturbance and its susceptibility to treatment.
7. From an investigational standpoint in rendering modifiable the bodily disturbances of various diseases.

The most suitable subjects for narcoanalysis under sodium amytal are those with disorders of personality adjustment of a relatively short duration. The drug is less useful in diagnosis or treatment of patients with rigid personalities or a long standing pattern of disability.

Sodium amytal is a highly useful tool in medicine but it is in no sense a specific or automatic agent. It is only of substantial value in the hands of a skillful physician who takes appropriate advantage of the state induced to gain diagnostic or therapeutic leverage.

FURTHER OBSERVATIONS ON THE ACTION OF DIBENAMINE IN HUMAN SUBJECTS

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Dibenzyl- β -chloroethyl amine (dibenamine), a compound related to the nitrogen mustards, has been claimed to possess certain sympatholytic properties in animals. In view of the clinical usefulness that an effective blocking agent for the adrenergic system would have, a study of the effect of the administration of dibenamine hydrochloride in seventy patients was made.

Only the intravenous route was found to yield consistent results. Not more than 4 to 6 mg./Kg. body weight were tolerated and transient toxic reactions occurred in almost all individuals. The most remarkable of these was a psychic disturbance consisting of repetitive preceptions of actual events and hallucinatory episodes which were associated with a disturbance of time sensations. Consciousness usually remained unimpaired and full insight into the psychotic state was present during the reaction. This bizarre alteration of mental function and of thought processes was noted in fifteen patients (21 per cent) but may have gone unnoticed in others.

The psychosis lasted for two to three hours while the height of the pharmacological action of dibenamine extended at least over a twenty-four-hour period. In some patients the response to standard sympathetic stimuli was altered for several days following a single injection.

- After the administration of dibenamine it was seen that some of the excitatory effects of sympathin E released by stimulation of the adrenergic system were altered or appeared completely blocked when tested in the resting patient following standard exercises or upon the intravenous administration of sympathomimetic compounds. Some of the expected responses to parenterally administered epinephrine remained unchanged or appeared potentiated by dibenamine.

The actions of the compound appear to be specifically directed toward certain excitatory effects of epinephrine but dibenamine cannot be

regarded as a neutralizer of the sympathetic nervous system in all respects. In the doses that can be safely administered to man dibenamine is regarded as a valuable pharmacological tool but appears to have limited therapeutic possibilities.

EXTENT OF VASODILATATION INDUCED IN DIFFERENT VASCULAR BEDS AFTER SYSTEMIC AUTONOMIC BLOCKADE WITH TETRAETHYLAMMONIUM

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In normotensive and hypertensive subjects injection of tetraethylammonium results in a temporary decrease in the total peripheral resistance as manifested by a reduction in mean arterial pressure and a maintained or increased cardiac output. The blood flow through vascular beds believed to be normally under some degree of vasomotor tone is markedly increased. The volume flow of blood in the hands and feet, as measured by the venous occlusion plethysmograph, increases significantly above resting levels following the administration of 500 mg. of the drug; it exceeds the levels achieved by other vasodilating drugs and may occur despite a marked decrease in arterial pressure. Blood flow seldom reaches the levels seen after sympathetic block with metycaine or after heat to the trunk suggesting that a complete autonomic blockade is not produced. On the other hand there is a rise in cutaneous circulation as judged by an increase in skin temperature of the hands and feet frequently with abolition of the temperature gradient. After sympathetic denervation of the extremity the blood flow is not further increased by administration of this drug. Induced vasoconstrictor reflexes in the hands and feet are reduced or abolished after tetraethylammonium. Blood flow in the forearm is only slightly increased after administration of the drug. Renal blood flow as measured by para-amino hippurate clearance is unaffected

despite variable reductions in arterial pressure in hypertensive and normal subjects. It is suggested that an increase in the blood flow through various vascular beds following tetraethylammonium depends on the presence of a neurogenic vasoconstrictor tone in these areas.

MECHANISM OF THE FALL IN ARTERIAL PRESSURE PRODUCED BY HIGH SPINAL ANESTHESIA IN PATIENTS WITH ESSENTIAL HYPERTENSION

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RAYMOND GREGORY, M.D.

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The problem has been studied by the simultaneous recording of arterial and venous pressures before and during high spinal anesthesia in five patients with normal blood pressures and in ten patients with essential hypertension.

The results demonstrate no constant correlation of changes in venous and arterial pressures. Arterial pressure may fall without any significant fall in venous pressure or may be preceded or followed by a fall in venous pressure. A fall in venous pressure may also occur without any significant fall in arterial pressure.

The conclusion is drawn that there is no cause and effect relationship for the decreases in arterial and venous pressure which may follow induction of high spinal anesthesia in patients with essential hypertension. It is further concluded that the fall in arterial pressure in such patients during high spinal anesthesia is probably not due to decreased cardiac output produced by diminished venous return.

CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY USING UNIPOLAR LIMB AND PRECORDIAL LEADS

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The roentgen diagnosis of right ventricular hypertrophy rests on less secure grounds than does that of left ventricular hypertrophy; therefore, other methods of diagnosis become of con-

siderable importance. The use of unipolar limb and precordial leads has provided a valuable means of recognizing right ventricular hypertrophy. With the present surgical approach to congenital pulmonary stenosis, the differentiation of this condition from other cyanotic congenital cardiac defects is especially important. Right ventricular hypertrophy is almost universally present in the tetralogy of Fallot, whereas early in the course of other lesions, such as patent interauricular septal defects, right ventricular hypertrophy may be absent. In patients with chronic pulmonary disease such as emphysema, pulmonary fibrosis, etc., it is often difficult to determine whether the condition is entirely pulmonary or whether chronic cor pulmonale has been superimposed. In this group of cases unipolar leads are of definite value.

Fifty cases of right ventricular hypertrophy have been studied with standard and unipolar leads and in many with further exploratory unipolar leads over the right anterior chest and abdomen. The patients with tetralogy of Fallot presented the most typical and complete pattern of right ventricular hypertrophy, whereas those with chronic cor pulmonale frequently had some of the typical electrocardiographic features absent, especially those from the right precordium.

The characteristic combination of findings in right ventricular hypertrophy include:

1. In leads from the right precordium and xiphoid, (1) a prominent, often tall R wave, (2) a small, often absent S wave, (3) a delayed onset of the intrinsic deflection (more than .03 second), (4) a depressed S-T segment and an inverted T wave, (5) an abnormally great ratio of the amplitude of R/S;

2. in leads from the left precordium, (1) a small R wave, (2) a deep S wave, usually greater than the R wave in the same lead, (3) a normal or shortened onset of the intrinsic deflection;

3. in the unipolar limb leads, (1) a prominent R wave in aV_R , (2) abnormal T waves in aV_F or aV_L depending on the position of the heart and (3) prominent P waves in aV_F .

The unipolar limb leads, in addition, were valuable in differentiating right axis deviation (as seen in the standard limb leads) due to a

vertically placed heart as the result of right ventricular hypertrophy. In some patients with chronic pulmonary emphysema or mitral stenosis the unipolar leads demonstrated that right axis deviation of $+90^\circ$ to 105° was due to a vertical heart and not to right ventricular hypertrophy. In others with similar standard leads right ventricular hypertrophy was demonstrated.

The importance of lead V_1 will be discussed since this lead frequently demonstrates the major abnormality. When right bundle branch is associated with right ventricular hypertrophy the abnormality may be seen in V_1 and not in V_2 .

ELECTROCARDIOGRAMS WITH POOR PROGNOSIS IN ACUTE CORONARY OCCLUSION

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This study comprises an analysis of the electrocardiographic findings in one hundred first attacks of acute myocardial infarction in subjects without antecedent heart disease. Comparison was made between fifty cases who succumbed within a period of six weeks and fifty cases who survived the attack.

Certain electrocardiographic features were found to occur preponderantly in the fatal cases and relatively infrequently in the surviving cases. In anterior infarction these included deep Q wave in lead I, the ABB pattern and bundle branch block. A review of cases reported in the literature indicates that these electrocardiographic changes are very commonly observed in ventricular aneurysm which is a sequel to extensive anterior infarction. When such changes occurred in surviving cases of anterior infarction they were usually transitory. Fatal cases of posterior infarction exhibited a much greater frequency of marked S-T segmental deviation, particularly marked depression in the precordial lead, bundle branch block and T changes in leads I and IV in addition to the usual Q_2 , Q_3 , T_2 , T_3 pattern.

In addition to these changes which appear to

indicate extensive infarction other findings occurred preponderantly in the fatal group. Among these were: electrocardiographic characteristics of combined anterior and posterior infarction, progressive changes other than the usual serial S-T and T evolution, electrical alternans, very low voltage of the QRS complex, prolongation of the Q-T interval, depression of the P-R interval and P changes suggesting associated auricular infarction, major arrhythmias such as auricular fibrillation, ventricular tachycardia and heart block and sinus tachycardia exceeding 110. Mention is made of other electrocardiographic findings which have been found to accentuate the gravity of acute myocardial infarction, such as Q and T changes in multiple chest leads and high P waves which appear to be associated with acute cardiac decompensation.

Among fatal cases of acute myocardial infarction over 80 per cent exhibited one or more of the findings described while in surviving cases the majority presented the simple anterior or posterior pattern. No significant difference was found in the incidence or mortality of anterior and posterior infarction *per se*.

RELATIVE EFFECTIVENESS OF VARIOUS DIURETICS IN CAUSING SODIUM EXCRETION IN PREGNANT WOMEN

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Patients in the last trimester of pregnancy have been placed on diets which furnished a constant intake of sodium and twenty-four-hour urine collections have been made for several weeks. After adequate periods of control observations, diuretic agents were administered and their effect of urine volume and sodium elimination were determined.

Mercurial diuretics (mercuhydrin and salyrgan) cause a marked loss of sodium chloride. This is accomplished by maintaining a relatively high concentration of sodium in the urine together with an increased urine volume. The sodium depletion after the administration of a mercurial drug may be so great that dietary

sodium is retained for a day or two in order to replenish the body stores.

Ammonium chloride in doses of 8 to 16 Gm. per day causes an acidosis in which sodium is eliminated in the urine. The initial effects may be more marked than those obtained on the second and third days so that prolonged treatment is relatively ineffective in causing a continuous loss of sodium. Urine volumes are not consistently increased.

Two hundred grams of glucose was administered intravenously in volumes ranging from 400 ml. to 4,000 ml. The effect on urinary volume is directly related to the volume of solution injected rather than to the concentration of the glucose. In no instance was the urinary volume increased sufficiently to account for all of the administered fluid. With increased urine volume there is a marked drop in sodium concentration so that no increase in sodium excretion could be demonstrated.

Aminophylline in large doses (7.5 gr. three times a day) has an effect similar to that of the mercurials, in that relatively high concentrations of sodium are maintained in the urine during the periods of increased volume output.

In two patients with toxemia of pregnancy, intravenous glucose solutions did not mobilize tissue fluids or sodium, whereas there was a marked increase in urine volume, sodium excretion and a loss of weight when they were given a mercurial drug. One eclamptic patient was given aminophylline after a six hour interval of anuria; a progressive diuresis started within one hour and the urine contained high concentrations of sodium.

FUNCTION OF THE STOMACH AS OBSERVED IN FISTULOUS HUMAN SUBJECTS, WITH SPECIAL REFERENCE TO THE ACTION OF DRUGS AND THE EFFECTS OF VAGOTOMY

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A human subject with a gastric fistula larger than that of Alexis St. Martin was studied in detail continuously for over five years. The

effects on the stomach of a large number of drugs and chemical agents were determined on this subject as well as on two other fistulous individuals. One of the latter was studied before and after bilateral supradiaphragmatic vagotomy.

The data obtained fell into five categories, allowing of the following inferences:

1. Secretory and motor activity in the stomach usually parallel one another and these gastric functions correspond closely to the blood flow through the organ. Drugs which inhibit gastric function induce a state of pallor and deturgescence in the stomach; drugs which stimulate gastric activity, on the other hand give rise to hyperemia and turgidity of the membrane.

2. The gastric mucous membrane is remarkably resistant to trauma during pallor and relative inactivity of the stomach. With hyperemia and engorgement, however, the membrane becomes far more vulnerable to physical insult, erosions and bleeding points resulting readily from minor traumas. When hyperemia and engorgement are intense and sustained a lowering of the pain threshold occurs so that ordinarily painless gastric contractions become painful.

3. By virtue of its protective covering of mucus the gastric mucosa, even when red and turgid, is comparatively resistant to the action of caustic chemical agents. It was found that various drugs, including emetics commonly

thought to be gastric irritants, actually do not exert an irritant effect on the stomach. Locally acting emetics exert their effects after passage into the duodenum.

4. Following vagotomy the stomach remained pale and inactive for several weeks. Slight hyperemia followed the ingestion of food but situational stimuli provocative of conflict with anger and resentment, accompanied by intense gastric hyperemia before operation failed to induce such a change after the vagus innervation had been interrupted.

5. In general, the effects on the stomach of a given quantity of any drug could not be predicted without reference to the prevailing state of the organ. Gastric inhibitors, for example, whose effects were readily demonstrable when the stomach was in an average state of engorgement and activity exerted no detectable effect when the stomach was turgid and over-active. Situational stimuli provocative of emotional changes were found to be of great importance in determining the state of the stomach. Profound alterations in gastric function associated with troublesome symptoms repeatedly followed the administration of placebos. Thus, the actions of the various drugs tested depended in large measure upon whether they reinforced or opposed the other influences acting at the same time.

Editorial

A Problem the Physician Must Face

THE past few decades have witnessed considerable progress in the understanding of organic disease. Development and refinement of methods of diagnosis and remarkable strides in chemotherapy have led to more accurate recognition of disease and to a steady decline in the list of fatal disorders. Also during this time almost all organized research in the medical field has been directed toward the solution of problems presented by organic disease. It is, of course, the result of these studies, including the development of new technics in biochemistry, physiology, pharmacology, bacteriology, etc., that such noteworthy progress has been made.

It is natural, therefore, that physicians trained during this period should have had their attention directed primarily toward organic disease. A glance at the current curricula of medical schools shows that this direction of the student's attention has not changed significantly, even today.

The broad increase in knowledge, however, has led inevitably to specialization in practice and this, in turn, has made it more difficult to deal with the patient as a whole. In the days before these advances in medicine, which resulted in the splitting-off of so many specialties, many of the older physicians had the opportunity to know their patients, their families and their activities, and were therefore in a position to appreciate more fully their emotional prob-

lems. The same is true of some physicians today but others have failed or refused to recognize these factors even though emotional disturbance is omnipresent. The war brought fresh emphasis upon the frequency and importance of the neuroses and focused attention sharply upon the need of more efficient recognition and therapy for this group.

When young physicians go into the practice of medicine, first during their training period in hospitals and later in their own offices, they find that only four or five of every ten patients have organic lesions related to, or sufficient to account for the patient's symptomatology. The remaining patients, for the most part, present symptoms resulting from emotional problems of varying degrees of severity. When faced with the responsibility for the care of this group, it is only natural that thoughtful physicians should feel that there has been a critical defect in this aspect of their training.

Perhaps many medical schools have already begun to consider means of meeting this problem, but the time is here for all of them, and indeed the whole medical profession, to face the problem squarely. If the majority of patients in the medical practitioner's office are there because of "functional disease" or symptoms produced by emotional disturbances, immediate steps are indicated to equip the practitioner and medical students with methods and technics

that will enable them to handle such problems more intelligently.

This does not mean that organic disease should be neglected or that research directed towards finding its cause and cure should be lessened. Rather, it means that a great deal more attention must be given to the rôle of emotional problems which produce disease and that students must be trained to understand and meet them. Of even greater importance is the fact that a far larger number of capable investigators must be attracted into this field with the hope that new approaches can be made to the study of the problems which are found there. Certainly all will agree that further study is indicated to define more clearly the rôle played by emotional disturbances in the production of disease symptomatology.

Psychiatrists have been developing and employing technics in the treatment of neuroses but it will be the internist, family physician or pediatrician who will be called upon to handle the large majority of mild neuroses and emotional disturbances. The importance of their being able to meet this problem and of knowing when to call for help is obvious. In the more severe neuroses the help of psychiatrists will be needed. The age of specialization has tended to segregate psychiatrists more than any other specialty, but the time has arrived for a much closer cooperation between the internist and the psychiatrist in solving these problems. Both can contribute and both have much to learn, but a freer exchange between the two groups will result in better care for the patient.

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Intercapillary Glomerulosclerosis*

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FOR years occasional diabetic patients have been observed who presented in varying degrees the clinical picture of albuminuria, nephrotic edema, hypertension, renal insufficiency and retinopathy. In the past such persons have been regarded as diabetic patients suffering from an independent renal or vascular disease which was usually diagnosed as chronic glomerulonephritis, nephrosis or diffuse arteriolar disease with hypertension.

In recent years it has become increasingly apparent that many, though certainly not all, such patients were in reality suffering from a more or less specific degenerative complication of diabetes, differing in certain respects from the common forms of renal and vascular disease observed among nondiabetic persons. This realization had its inception in 1936, when Kimmelstiel and Wilson¹² described lesions of the glomeruli of the kidneys of a group of diabetic patients who during life had presented some or all of the clinical features mentioned in the preceding paragraph. To these lesions Kimmelstiel and Wilson applied the term "intercapillary glomerulosclerosis" because the lesions were characterized by spherical or diffuse hyalin-like masses apparently lying between the capillaries of the glomerular tuft. Since then numerous additional studies^{1,2,4,7,10,11,14,19-21} and case reports^{3,5,6,8,9,15-18,22} have confirmed in gen-

eral the original observations of Kimmelstiel and Wilson and have lent support to the idea that intercapillary glomerulosclerosis merits inclusion with retinopathy and neuropathy as a degenerative complication of diabetes. In addition it has become apparent that intercapillary glomerulosclerosis is not always associated with the complete clinical syndrome which was observed in the original cases described by Kimmelstiel and Wilson.

Certain problems related to intercapillary glomerulosclerosis still need clarification. Prominent among them are the questions of the specificity of the lesion for diabetes mellitus, the clinical criteria for its recognition during life, the frequency of its occurrence among diabetic patients, and the relation of the associated changes in the ocular fundi to the lesions in the kidneys. Our purpose in this paper is to present certain observations which have a bearing on these and other relevant points.

MATERIAL AND METHODS

The pathologic material used in this study was as follows: (1) the kidneys of 313 diabetic patients; (2) the kidneys of eighty-one non-diabetic patients on whom a clinical diagnosis of chronic glomerulonephritis had been made; (3) the kidneys of 134 non-diabetic patients whose death had resulted from hypertension and its complica-

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tions; (4) the kidneys, spleen, adrenals, liver and pancreas in twelve cases of amyloidosis; (5) the spleen, adrenals, liver and pancreas in each case from the foregoing groups in which there were advanced lesions of intercapillary glomerulosclerosis; (6) the kidneys of 2,022 routine necropsy cases observed from 1940 to 1943, inclusive, some of them included in the foregoing groups.

In the course of the study a variety of different histologic stains was employed. Specific reference will be made to some of these later.

A clinical study was made of the records of all cases, diabetic and non-diabetic, in which the renal lesions of intercapillary glomerulosclerosis were found. A similar study was made of the records of a group of diabetic patients whose kidneys did not exhibit the lesions, for comparison with the diabetic patients whose kidneys did exhibit the lesions.

HISTOLOGIC FINDINGS

Types and Incidence of Lesions. It is reasonable to suppose that the lesions of intercapillary glomerulosclerosis pass through a long period of evolution from the time of their inception until they reach an advanced stage. Consequently, the histologic criteria on which to base a diagnosis of intercapillary glomerulosclerosis are not readily defined and the dividing line between kidneys which are said to exhibit the lesions and those which are said not to exhibit them must of necessity be arbitrary. The varying criteria employed probably account for the wide variation in incidence of the lesions (from approximately 20 per cent^{4,11} up to 63.7 per cent¹⁴) in diabetic necropsy material reported by various workers.

Briefly stated, in this study a diagnosis of intercapillary glomerulosclerosis was made if hyalin-like, globular, deeply staining lesions like those originally described by Kimmelstiel and Wilson (Fig. 1), or small

deeply staining, club-shaped masses situated in the midst of a diffuse thickening along the axis of the lobule (Fig. 2) could be demonstrated. It was believed that the former type of lesion represented an advanced stage in the development of intercapillary glomerulosclerosis, and that the latter represented an early stage. All other kidneys, including a large group with mild, diffuse thickening, possibly of the intercapillary tissue, were classified as negative for intercapillary glomerulosclerosis. In most instances, the lesions designated as intercapillary glomerulosclerosis were readily identifiable in sections stained with hematoxylin and eosin.

The incidence of intercapillary glomerulosclerosis in 313 cases of diabetes was 19.5 per cent (sixty-one cases). Among the sixty-one cases of intercapillary glomerulosclerosis, the lesions were classified as "early" in thirty-one cases, and "advanced" in thirty cases. Among eighty-one cases of glomerulonephritis affecting non-diabetic patients, the incidence was 12.3 per cent (ten cases). The lesions in seven of the cases in this group were early, and in three they were advanced. Among 134 cases in which the death of non-diabetic patients was due to hypertension and its complications, the incidence was 5.2 per cent (seven cases); in this group there were no advanced lesions.

Association of Renal Arteriosclerosis with Intercapillary Glomerulosclerosis. All the kidneys, whether from diabetic or non-diabetic patients, in which lesions of intercapillary glomerulosclerosis were found exhibited some arteriosclerosis. In many instances it was minimal. Not only the afferent and efferent arterioles of the glomerulus were involved, but also the interlobular arterioles. In cases of glomerulonephritis the sclerosis often had the appearance of obliterative endarteritis, apparently due to previous destruction of the glomeruli. In cases of hypertension

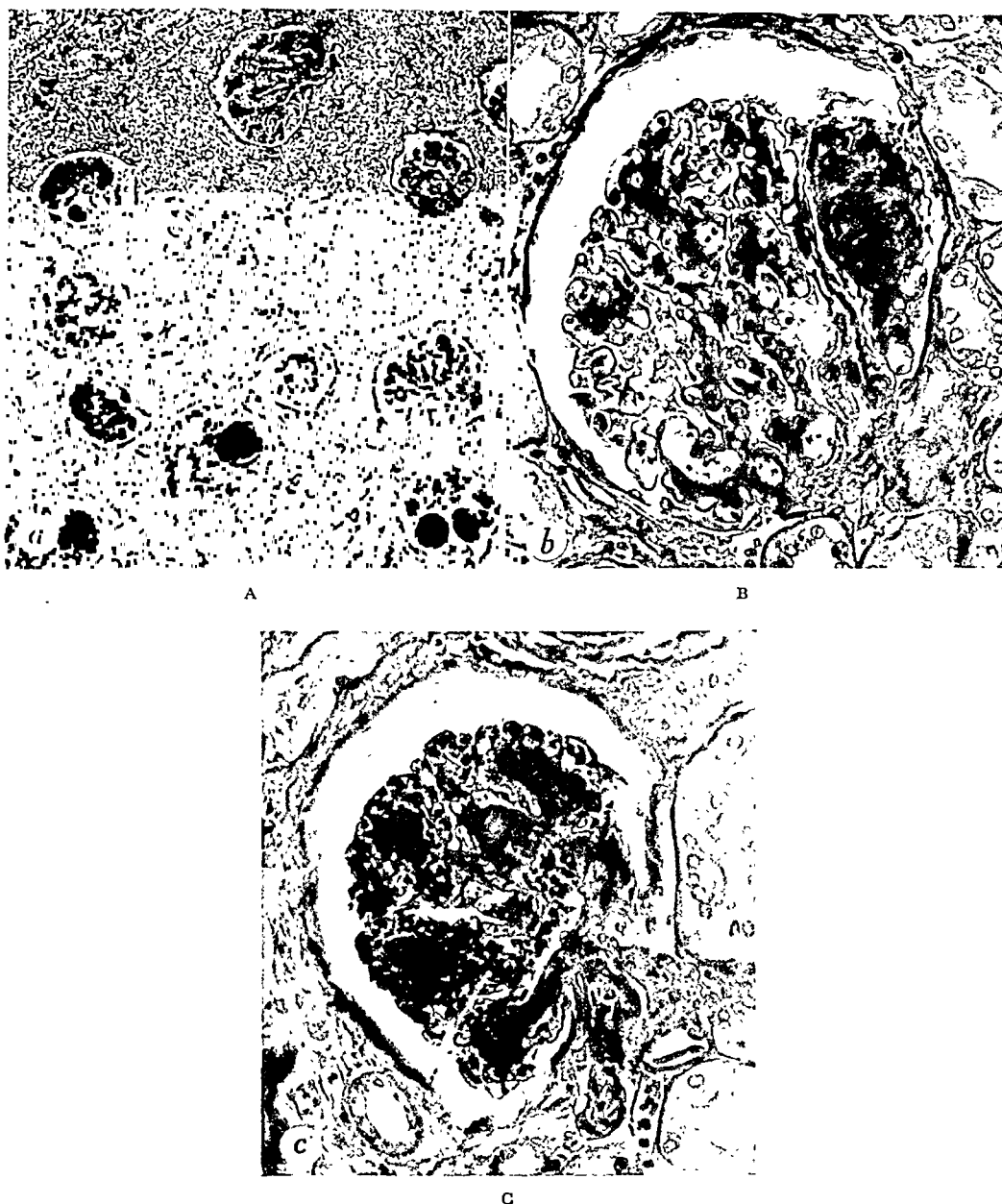


FIG. 1A. Kidney of a diabetic patient, containing many advanced lesions of intercapillary glomerulosclerosis ($\times 55$); B, glomerulus from kidney of a diabetic patient. There is a large lesion in the center of a lobule, surrounded by a ring of patent capillaries, and many other smaller lesions throughout the glomerulus ($\times 275$); C, glomerulus from kidney of a diabetic patient, containing several advanced lesions. There is considerable sclerosis of the afferent arteriole ($\times 260$).

there were often thickened arteriolar walls typical of malignant hypertension. In the kidneys from diabetic patients there was usually a patchy thickening of the arteriolar walls with considerable hyalinization. While there was at least a rough parallelism be-

tween the degree of arteriolosclerosis and the severity of the glomerular lesions in most cases, some glomerular lesions were observed without significant degrees of associated arteriolosclerosis. It, therefore, seems unlikely that arteriolosclerosis is the sole



FIG. 2. Glomerulus from kidney of a diabetic patient, showing small, deeply staining, club-shaped masses, classified as early intercapillary glomerulosclerosis ($\times 300$).

etiologic factor in the production of intercapillary glomerulosclerosis.

Differentiation of Intercapillary Glomerulosclerosis from the Glomerular Lesions of Chronic Glomerulonephritis and Amyloidosis. The resemblance between the glomerular lesions in intercapillary glomerulosclerosis, chronic glomerulonephritis and amyloidosis is due to the fact that in each of them, large portions of the glomerulus may consist of a substance which stains homogeneously. As a rule it was not difficult to distinguish between intercapillary glomerulosclerosis and the usual lesions of chronic glomerulonephritis. In the latter disease the sclerosing, hyalinizing process caused a rather marked, diffuse involvement throughout a glomerulus or a large portion of it. Sharply defined spherical lesions like those of intercapillary glomerulosclerosis were not commonly seen. If a single homogeneous mass of material was found, it usually involved at least an entire lobule, and no patent capillaries remained. Also, the relatively mild alterations of renal architecture in most cases of intercapillary glomerulosclerosis contrasted strikingly with the widespread

destruction and distortion of the normal structures of the kidneys in cases of chronic glomerulonephritis. In the latter condition many glomeruli were completely hyalinized, and throughout the sections atrophic and degenerating tubules were seen.

There were, however, the ten cases of glomerulonephritis, previously diagnosed as such both clinically and at necropsy, in which lesions were found which were indistinguishable from those of intercapillary glomerulosclerosis. In only three of these were the lesions typical of advanced intercapillary glomerulosclerosis. (Fig. 3.) They had the same shape, staining characteristics and general appearance as those observed in the kidneys of diabetic patients. The lesions occurred with too much regularity throughout all the sections studied to be regarded as ordinary lesions of chronic glomerulonephritis which by chance had assumed the appearance of lesions of intercapillary glomerulosclerosis. This evidence suggests that the process which gives rise to intercapillary glomerulosclerosis may occur in the absence of clinically recognizable diabetes.*

Sections of the kidneys from twelve cases of amyloidosis, in six of which there was marked involvement of the glomeruli (Fig. 4), were compared with sections of kidneys from four cases of diabetes in which there were advanced lesions of intercapillary glomerulosclerosis. A variety of histologic stains, including stains for amyloid, was employed. There was not sufficient difference in the staining reactions of the glomerular lesions in the two conditions to permit positive differentiation. Sections stained with Gomori silver showed a greater lamination of the glomerular lesions of intercapil-

* It is of considerable interest, and possibly of some significance, that there was a family history of diabetes in two of the three cases in which a clinical diagnosis of chronic glomerulonephritis had been made but in which the kidneys exhibited lesions typical of advanced intercapillary glomerulosclerosis.

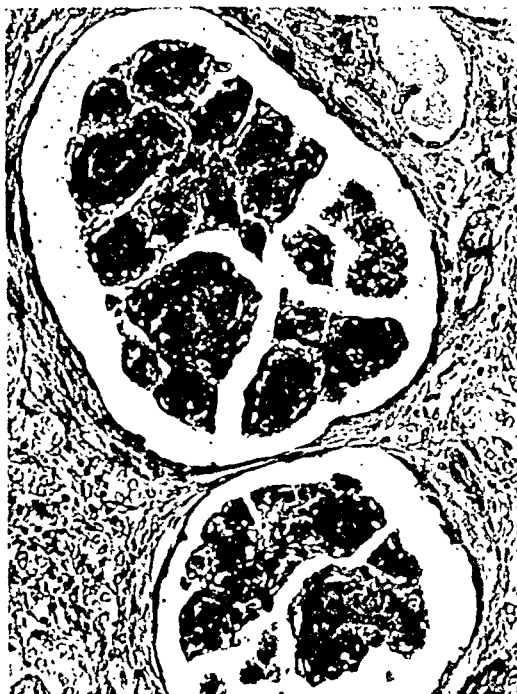


FIG. 3. Glomeruli from kidney of a non-diabetic patient. The clinical diagnosis in this case was chronic glomerulonephritis. The hyaline masses, surrounded by patent capillaries, have virtually the same appearance and staining reactions as the lesions of intercapillary glomerulosclerosis observed in diabetes ($\times 200$).



FIG. 4. Kidney of a non-diabetic patient who had amyloidosis. In the glomeruli are several masses which, seen alone, might be mistaken for intercapillary glomerulosclerosis ($\times 285$).

lary glomerulosclerosis than of amyloidosis, but reliable differentiation on this basis alone was not possible. More positive differentiation was possible when other tissues were studied. In amyloidosis either the spleen or the adrenals or both were involved as severely as the kidneys, while this was not true in intercapillary glomerulosclerosis.

On the basis of the foregoing indirect evidence it seems unlikely that the substance of the lesions of intercapillary glomerulosclerosis is the ordinary variety of what is called amyloid. On the other hand, the fact that, when only the kidneys were considered, it was difficult to distinguish intercapillary glomerulosclerosis from amyloidosis makes one suspect that the degenerative material may be an amyloid-like compound.

Association of Intercapillary Glomerulosclerosis and Hyalinization of the Pancreatic Islets. In

the three cases of glomerulonephritis in which there were advanced lesions of intercapillary glomerulosclerosis in the kidneys there was no hyalinization of the islets. Among twenty-nine cases of diabetes in which there were advanced lesions of intercapillary glomerulosclerosis, twelve (41 per cent) exhibited varying degrees of hyalinization of the islets. Since this incidence of hyalinization of the islets is no higher than that found by Warren²⁶ in a large number of necropsies on diabetic patients, it appears that there is no important relation between the pancreatic and the renal lesions. Incidentally, the data suggest that intercapillary glomerulosclerosis, at least as here defined, is not a more reliable criterion than hyalinization of the islets for the postmortem diagnosis of diabetes mellitus. Laipply, Eitzen and Dutra,¹⁴ on the other hand, considered intercapillary glomerulosclerosis to be the most common pathologic finding which is pathognomonic of diabetes.

COMPARISON OF CLINICAL FEATURES OF DIABETES MELLITUS WITH AND WITHOUT INTERCAPILLARY GLOMERULOSCLEROSIS

As previously stated, the lesions of intercapillary glomerulosclerosis probably pass through a long period of development from their beginning until they reach an advanced stage. It seems likely that the clinical manifestations of the condition would depend on its severity and therefore, if the lesions are progressive, on its duration; that is, very early lesions involving only a small portion of each glomerulus would not disturb renal function, while advanced lesions might be expected to produce the complete clinical syndrome originally described by Kimmelstiel and Wilson, including albuminuria, nephrotic edema, hypertension, renal impairment and changes in the ocular fundi.

Furthermore, if intercapillary glomerulosclerosis is in truth a lesion which occurs for the most part in diabetic persons, it must represent a different pathologic process from those which give rise to the usual forms of renal disease among non-diabetic persons. It might, therefore, be expected that its clinical manifestations would differ in some respects from those of the common chronic forms of renal disease observed among non-diabetic persons.

The analysis of clinical and pathologic data from cases of diabetes, chronic glomerulonephritis, and diffuse arteriolar disease with hypertension suggests that the foregoing lines of reasoning have some foundation in fact. In the material which follows an effort is made to compare the clinical picture of diabetes without intercapillary glomerulosclerosis with that of diabetes with this renal lesion, and later to point out differences between the latter group and non-diabetic patients who were found to have the lesions of intercapillary glomerulosclerosis in association with chronic glomerulonephritis or diffuse arteriolar disease with hypertension.

Age and Sex. Lesions of intercapillary glomerulosclerosis were found among diabetic patients ranging from eighteen to seventy-eight years of age. The lesions occurred with the greatest frequency in the more advanced age groups, the average age being sixty years. The average age of diabetic patients without lesions was about the same (fifty-nine years). In the 313 cases of diabetes studied pathologically, 206 patients were men and 107 were women. The incidence of intercapillary glomerulosclerosis was almost twice as great among the women (twenty-nine instances, or 27.1 per cent) as among the men (thirty-two instances, or 15.5 per cent).

Duration, Severity and Control of Diabetes. The data support the hypothesis that both the occurrence and the severity of the lesions bear a direct relationship to the known duration of the diabetes. In the cases in which advanced lesions were present, the average known duration of diabetes was 11.2 years; in those cases with mild lesions it was 8.1 years, while in the cases without lesions it was 5.2 years. It is probably significant that, among those cases in which the known duration of diabetes was short, but lesions were nonetheless present, the diabetes was always mild and might, therefore, have been present without symptoms for years before it became clinically apparent.

Inasmuch as the average age of the patients exhibiting lesions was sixty years, it would be anticipated that the majority of the patients would have had diabetes of relatively mild degree. This proved to be the case. The average severity of the diabetes was between grade 2 and grade 3, using a system of grading in which 1 is the mildest degree of diabetes and 4 is the most severe.* The average severity in the group

* The system of grading is an arbitrary one employed by the Section on Metabolism Therapy of the Mayo Clinic. *Grade 1* is the designation applied to those cases of mild diabetes in which glycosuria is controlled simply by omitting concentrated sweets from the diet. *Grade 2*

of cases without lesions was the same as that in the group with lesions, suggesting that there is no correlation between the severity of the diabetes and the presence of intercapillary glomerulosclerosis.

Control of diabetes is difficult to estimate in any given case, especially since it is likely to vary from time to time. The impression was gained from a review of the histories of patients with and without intercapillary glomerulosclerosis that there was little difference in the degree of control of the disease in the two groups.

Hypertension. Using a systolic blood pressure of more than 150 mm. of mercury as an arbitrary criterion of hypertension, it was found that 60 per cent of the diabetic patients with intercapillary glomerulosclerosis were hypertensive, as compared to 32 per cent of the diabetic patients without intercapillary glomerulosclerosis. The incidence of hypertension in both groups was 40 per cent, which is in close agreement with the incidence of 39 per cent mentioned by Kramer.¹³ It is apparent that hypertension is not an essential part of the clinical syndrome associated with intercapillary glomerulosclerosis.

Cardiac Decompensation. Some writers^{16,17} have called attention to a relatively high incidence of cardiac decompensation among diabetic patients suffering from intercapillary glomerulosclerosis. Our data show the same trend. The incidence of cardiac decompensation among the diabetic patients with intercapillary glomerulosclerosis was 33 per cent, as compared to 11 per cent in those without intercapillary glomerulosclerosis.

includes those cases of mild diabetes in which glycosuria is controlled by adherence to a quantitative diet containing approximately 150 Gm. of carbohydrate, without the use of insulin. *Grade 3* includes cases of somewhat more severe diabetes in which satisfactory control cannot be maintained by adherence to an adequate diet alone, but in which, in addition, up to 30 units of insulin daily is necessary. *Grade 4* is the term applied to cases in which more than 30 units of insulin is required daily.

Edema. This occurred to some degree in 47 per cent of the patients with intercapillary glomerulosclerosis, and in 19 per cent of those without it. In many of the cases of intercapillary glomerulosclerosis in which edema was present, it was associated with cardiac decompensation. In only four of twenty-nine cases of intercapillary glomerulosclerosis in which edema was present could it be classified as the nephrotic type. It is thus evident that edema is not a necessary feature of the syndrome associated with intercapillary glomerulosclerosis, and that when edema does occur it is not always of the nephrotic type.

Association of Intercapillary Glomerulosclerosis with Other "Degenerative" Complications of Diabetes. If intercapillary glomerulosclerosis is in truth a more or less specific complication of diabetes, it should be fairly frequently associated with other complications which are known to be related to diabetes. The following data relative to its association with arteriosclerosis obliterans and gangrene, diabetic neuropathy and diabetic retinopathy tend to substantiate this hypothesis.

(1) *Arteriosclerosis obliterans and gangrene:*—Arteriosclerosis obliterans and gangrene were found to occur far more frequently among diabetic patients with intercapillary glomerulosclerosis than among those without it. Among the cases with lesions in the kidneys, decrease in the strength of pulsations of the arteries of the feet was recorded in 51 per cent, as compared to 22 per cent in the cases without lesions. These figures are not to be regarded as an accurate indication of the actual frequency of occlusive arterial disease, as there was no record of arterial pulsations in some of the cases, but they are probably a valid indication of the relative frequency of this complication in the two groups. Gangrene of the lower extremities occurred in 12 per cent of the patients who had inter-

capillary glomerulosclerosis and in 4 per cent of those who did not have it.

(2) Diabetic neuropathy:—This complication also occurred more frequently among patients having intercapillary glomerulosclerosis than among those not having it.

advance through successive stages in the evolution of a common basic disturbance. They observed the following groups of retinal lesions specifically associated with diabetes mellitus: Group 1, hemorrhages only; Group 2, hemorrhages with punctate

TABLE I

ASSOCIATION OF VARIOUS TYPES OF RETINOPATHY WITH INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETIC PATIENTS; COMPARISON WITH FINDINGS IN THREE SERIES OF LIVING DIABETIC PATIENTS

	Necropsy Cases, This Series		Living Diabetic Patients		
	Intercapillary Glomerulosclerosis Present	Intercapillary Glomerulosclerosis Absent	Series 1921 ²⁴	Series 1934 ²⁵	Series 1945 ²³
Diabetic retinopathy: hemorrhages only, per cent.	9.4	14.0	3.7	5.5	9.9
Diabetic retinopathy: hemorrhages with punctate exudates, per cent.	25.0	3.8	0.7	6.3	8.8
Diabetic retinopathy: hemorrhages with punctate and cotton-wool-like exudates, per cent.	25.0	1.2	2.6	2.9	4.6
Diabetic retinopathy: venous disease and proliferating retinopathy, per cent.	6.3	0	0	1.9	4.1
Hypertensive retinopathy, per cent.	3.1	3.8	1.3	1.1	0.7
Total cases with retinopathy, per cent.	68.8	22.8	8.3	17.7	30.6*
Number of cases.	32	79	300	1,052	1,021

* Includes 2.5 per cent with retinopathy which was thought to be due wholly or in part to "toxic" factors, not separately listed in the table.

The recorded incidence in the two groups was 23 per cent and 5 per cent, respectively.

(3) Diabetic retinopathy:—While retinal changes associated with intercapillary glomerulosclerosis have been mentioned by several writers, references to this aspect of the problem have to date been rather brief. For the most part, the retinopathy which has been described has been of a type predominantly related to hypertension. The data which follow indicate that the retinal lesions observed in association with intercapillary glomerulosclerosis are predominantly diabetic in type.

Wagener, Dry and Wilder²⁵ pointed out that diabetic retinopathy is a progressive condition in which the characteristic lesions

exudates; Group 3, hemorrhages with punctate and cotton-wool-like exudates; Group 4, venous disease, with any of the foregoing: (1) without proliferation, and (2) with proliferation.

For purposes of study of retinopathy, the records of 111 cases of diabetes in which necropsy was performed between 1937 and 1943 were reviewed because in all of these examination of the ocular fundi had been done shortly before death, and most of the examinations were performed by one of us (H. P. W.). Of the 111 patients, thirty-two had intercapillary glomerulosclerosis and seventy-nine did not. The incidence of retinopathy among the patients who had intercapillary glomerulosclerosis and among

those who did not have it is summarized in Table I. For purposes of comparison, data on the incidence of retinopathy in a group of living diabetic patients reported by Wagener and Wilder²⁴ in 1921, another group reported by Wagener, Dry and Wilder²⁵ in 1934, and a third group reported by Wagener²³ in 1945 are also given. It is to be noted that the highest incidence of retinopathy was among the necropsy cases having intercapillary glomerulosclerosis (68.8 per cent). In this group the incidence of retinopathy was higher among those cases in which advanced lesions were present in the kidneys (86 per cent) than it was among those cases in which early lesions were present (53 per cent). A considerably lower incidence of retinopathy was noted among the necropsy cases in which intercapillary glomerulosclerosis was not present (22.8 per cent).

A surprisingly high incidence of retinopathy was noted among the group of living diabetic patients examined during 1944 and reported by Wagener in 1945. It is cause for alarm that the incidence of retinopathy in Wagener's 1945 group (30.6 per cent) was almost twice that reported by Wagener, Dry and Wilder (17.7 per cent) in 1934 and the latter figure was more than twice that noted in the 1921 series of Wagener and Wilder (8.3 per cent).

In practically all cases of intercapillary glomerulosclerosis in which retinopathy was present there were lesions in the ocular fundi typical of diabetes. Purely hypertensive retinopathy was present in only one of the thirty-two cases, whereas lesions typical of diabetes were present in twenty-one cases. In many of the latter cases there were changes in the fundi attributable to both diabetes and hypertension; namely, the punctate hemorrhages and waxy exudates characteristic of diabetic retinopathy, and the superficial hemorrhages, cotton-wool patches, arteriolosclerosis and spastic nar-

rowing of the retinal arterioles characteristic of hypertensive retinopathy. In some instances the changes which are characteristic of diabetes were found only after careful examination of the peripheral portion of the retina.

Inasmuch as the same types of retinopathy, with the possible exception of venous disease, occurred among diabetic patients with and without intercapillary glomerulosclerosis, and inasmuch as in some cases of intercapillary glomerulosclerosis retinopathy was not present, it is obvious that no one type is specifically indicative of the presence of intercapillary glomerulosclerosis. It is also evident that the predominant cause of the retinal changes observed in intercapillary glomerulosclerosis is diabetes rather than renal disease or hypertension.

It is of interest that the incidence of association of the more complex types of retinopathy (that is, groups 3 and 4) with intercapillary glomerulosclerosis was high. Thus, all of the diabetic patients who were found during life to have retinopathy of type 4 were later proved at necropsy to have intercapillary glomerulosclerosis. Likewise, retinopathy of type 3 also had a high incidence of association with intercapillary glomerulosclerosis (eight of nine cases). Retinopathy of types 1 and 2 was less frequently associated with intercapillary glomerulosclerosis. It is thus apparent that, the more complex and advanced the retinopathy, the more likely is its association with intercapillary glomerulosclerosis.

In summary, it can be stated that the retinopathy which occurs in association with intercapillary glomerulosclerosis almost always includes changes which are attributable to diabetes; that retinopathy is far more common among diabetic patients who have intercapillary glomerulosclerosis than it is among those who do not have it; and that the more advanced types of diabetic retinop-

athy are more or less regularly associated with intercapillary glomerulosclerosis.

Laboratory Findings. (1) *Albuminuria:*—This was observed practically universally among the diabetic patients who later were proved at necropsy to have intercapillary glomerulosclerosis. It occurred in all the cases in which severe renal lesions were present, and in 90 per cent of the cases in which early lesions were present, or in 95 per cent of the entire group. Furthermore, there was a positive correlation between the severity of the renal lesions and the degree of albuminuria. Seventy-six per cent of the diabetic patients who did not have intercapillary glomerulosclerosis exhibited albuminuria of some degree, but it was, on the average, of much lower grade than that of the patients who had intercapillary glomerulosclerosis.

(2) *Serum proteins:*—There were only four determinations of total serum proteins among the cases of intercapillary glomerulosclerosis, the values being 6.7, 6.6, 5.5 and 4.3 Gm. per 100 cc. of serum. These meager data, and the fact that this determination was not made more frequently, suggest that hypoproteinemia of marked degree is probably not a common manifestation of intercapillary glomerulosclerosis.

(3) *Renal function:*—Among fifty-five cases of intercapillary glomerulosclerosis in which data were available the blood urea was elevated above the maximal normal level of 40 mg. per 100 cc. in thirty-five (64 per cent), as compared to forty-eight (53 per cent) of ninety-one cases in which intercapillary glomerulosclerosis was not present. The latter group may include a considerable number of selected cases in which determinations of the blood urea were made because the clinicians suspected some abnormality for one reason or another. The average severity of the azotemia differed little in the two groups.

The data on specific gravity of the urine

are no more clear-cut. In the collection of these data specimens of urine were chosen which contained no more than traces of glucose, because of the effect of greater amounts of this substance on specific gravity. There was no significant difference in the average specific gravity in the cases in which intercapillary glomerulosclerosis was present (1.022) and in those in which it was not present (1.023).

The foregoing data indicate, at least, that impairment of renal function is not a universal accompaniment of intercapillary glomerulosclerosis.

(4) *Anemia:*—This was not a common finding among the cases of intercapillary glomerulosclerosis. In only two cases was the erythrocyte count as low as 2,800,000 per c. mm. of blood and in the majority of cases the value was 4,000,000 or more per c. mm. The average erythrocyte count in the cases in which there was intercapillary glomerulosclerosis was 4,100,000, as compared to 4,200,000 in the cases in which it was not present. The average values for hemoglobin in the two groups were 12.1 and 13.2 Gm. per 100 cc. of blood, respectively.

Causes of Death. Disease of the cardiovascular system accounted for the death of thirty-two (52.5 per cent) of the sixty-one diabetic patients who were found at necropsy to have intercapillary glomerulosclerosis. The thirty-two deaths included fourteen due to congestive heart failure, ten due to gangrene, five due to cerebral vascular accidents, two due to myocardial infarction and one due to cardiac dilatation. The only other common cause of death in this group was carcinoma (eight cases, 13.1 per cent). In only one case was death thought to be due to renal insufficiency *per se*.

Among the diabetic patients who were found at necropsy not to have intercapillary glomerulosclerosis, disease of the cardiovascular system accounted for 30.1 per cent of the deaths. Carcinoma was a common

cause of death in this group also (28.5 per cent).

CLINICAL FEATURES OF CASES OF CHRONIC
GLOMERULONEPHRITIS WITH LESIONS
RESEMBLING INTERCAPILLARY
GLOMERULOSCLEROSIS

As previously stated, among eighty-one cases in which the disease had been diagnosed clinically as chronic glomerulonephritis, there were three in which the lesions of the glomeruli were indistinguishable morphologically from those of advanced intercapillary glomerulosclerosis, and seven in which the lesions were similar to those of early intercapillary glomerulosclerosis. The clinical behavior of these ten cases is of theoretical interest because of its bearing on the question of the specificity of intercapillary glomerulosclerosis for diabetes. If the clinical course of these patients closely resembled that of the diabetic patients who had intercapillary glomerulosclerosis, it would lend support to the hypothesis that the lesions of the glomeruli in the two groups were identical, and therefore not associated solely with diabetes. On the other hand, if their clinical course were quite different from that of the diabetic patients, it might be surmised that the lesions of the glomeruli in the patients with chronic glomerulonephritis had merely an accidental morphologic resemblance to those of intercapillary glomerulosclerosis, but in view of their different clinical behavior actually represented a different pathologic process.

A study of the clinical records of the eighty-one patients who had chronic glomerulonephritis disclosed no significant difference between the ten who had lesions of the glomeruli resembling intercapillary glomerulosclerosis and the seventy-one who did not have such lesions. A comparison of the records of the ten who had such lesions with those of the diabetic patients who had intercapillary glomerulosclerosis showed

that the two groups were superficially similar: many of the patients in both groups had hypertension, albuminuria, edema and retinopathy. There were, however, several important differences. The average age of the diabetic patients was fifty-eight years, while the average age of the patients who had chronic glomerulonephritis was only thirty-two years. In the cases of glomerulonephritis edema was a more prominent feature than in the cases of diabetes. Among the diabetic patients the retinopathy in almost all cases, as already noted, included some features of diabetic retinopathy, while among the patients who had glomerulonephritis the retinopathy was of hypertensive type.

The clinical course of the two groups of cases was quite different. The terminal illness of the patients who had glomerulonephritis was of one to four months' duration, whereas the diabetic patients lived for months to years after the clinical syndrome associated with intercapillary glomerulosclerosis was fully developed. The cause of death of the patients who had glomerulonephritis was almost always renal or cardiac failure, while the causes of death among the diabetic patients, as already noted, were much more varied. These observations suggest that intercapillary glomerulosclerosis associated with diabetes is a much more benign process than glomerulonephritis with renal lesions resembling intercapillary glomerulosclerosis.

The laboratory findings in the two groups also showed significant differences. Among the cases of glomerulonephritis the anemia was more severe, the hemoglobin averaging only 7.2 Gm. per 100 cc. of blood and the erythrocyte count 2,400,000 per c. mm. of blood; the blood urea was much higher, the average value being 298 mg. per 100 cc.; the specific gravity of the urine was significantly lower, the average being 1.013; albuminuria was more intense, and the

total serum protein was probably lower, averaging 4.6 Gm. per 100 cc.

On the basis of clinical evidence, therefore, it seems probable that the lesions of the glomeruli in the ten cases of glomerulonephritis, while having a morphologic resemblance to intercapillary glomerulosclerosis as seen in diabetic patients, probably represented a different pathologic process.

CLINICAL FEATURES OF CASES OF HYPERTENSION WITH RENAL LESIONS RESEMBLING INTERCAPILLARY GLOMERULOSCLEROSIS

No advanced lesions of intercapillary glomerulosclerosis were found among the cases of hypertension. Early lesions were found in seven cases. There was so much variation in clinical and laboratory findings among these cases that comparison with the cases of intercapillary glomerulosclerosis among diabetic patients was difficult. All seven had hypertension, retinopathy, albuminuria and azotemia. In none of them did the retinopathy include changes attributable to diabetes, and in three of them the retinopathy was that of malignant hypertension. The cause of death in all seven cases was renal or cardiac failure.

From these data it is not possible to draw any conclusions about the identity of the glomerular lesions in these cases of hypertension and those in the diabetic patients who had intercapillary glomerulosclerosis.

COMMENT

Incidence. The wide variations in the reported incidence of intercapillary glomerulosclerosis among diabetic patients who have died depend for the most part on different definitions of the lesion. The incidence of 19.5 per cent found in this series is based on a definition of the lesion which probably excludes some cases in which there are mild lesions. The direct correlation between incidence of lesions and duration of

diabetes suggests that intercapillary glomerulosclerosis will be a more and more frequent clinical problem as the average duration of diabetes is increased by better therapy and more effective education of the patient in diabetic care. Unfortunately, there is little in the present study or in other studies to suggest that this complication can be prevented in most instances by careful control of diabetes.

The reported incidence of intercapillary glomerulosclerosis among non-diabetic persons also has varied a great deal. Most writers agree, however, that it is relatively low as compared to the incidence among diabetic patients and that the lesions observed in non-diabetic persons are usually mild. Several other reports are in agreement with our observation that after diabetes mellitus the second highest incidence is in cases in which the clinical diagnosis is chronic glomerulonephritis. In our series, the only non-diabetic cases in which there were advanced lesions were cases of chronic glomerulonephritis.

Specificity of the Lesion for Diabetes Mellitus. The fact that lesions of the glomeruli which are indistinguishable morphologically from intercapillary glomerulosclerosis occur in other conditions than diabetes mellitus forces one to the conclusion that the lesion is not a degenerative complication which is specifically related to diabetes. It is noteworthy, however, that the incidence of the lesion in diabetes is much greater than in any other condition,* and that advanced lesions occur rarely except among diabetic patients. Further, it is noteworthy that in chronic glomerulonephritis, the only other condition in which lesions were found more than just occasionally, the clinical manifes-

*The data of Horn and Smetana¹¹ are not in agreement with this statement. Their figures on incidence of intercapillary glomerulosclerosis are: diabetes mellitus, 22.9 per cent; arteriolar nephrosclerosis without diabetes, 25.4 per cent; glomerulonephritis, 6.9 per cent; arteriolar nephrosclerosis with diabetes, 59.1 per cent.

tations associated with the lesion were more severe than in diabetes, even though the lesions themselves were, on the average, milder. This curious observation suggests the possibility that the presence of lesions resembling intercapillary glomerulosclerosis is a fortuitous circumstance in some cases of glomerulonephritis, and is not traceable to the same pathologic process as in diabetes.

Clinical Criteria for the Recognition of Intercapillary Glomerulosclerosis during Life. At the present time, there are no certain means available for establishing a diagnosis of intercapillary glomerulosclerosis during life. As emphasized by Bell,⁴ there are no definite clinical features by which diabetes with intercapillary glomerulosclerosis can positively be distinguished prior to necropsy from diabetes without intercapillary glomerulosclerosis. Diabetes with intercapillary glomerulosclerosis may have many clinical manifestations in common with diabetes without intercapillary glomerulosclerosis. For example, the presence of minor degrees of albuminuria alone in a diabetic patient is not a reliable indication that intercapillary glomerulosclerosis, as here defined, is present. For the most part, however, the mild lesions are the least likely to give rise to clinical features of diagnostic significance. The presence of advanced lesions, on the other hand, can be predicted with considerable certainty in patients who have diabetes mellitus (particularly diabetes of long duration), albuminuria, hypertension, renal insufficiency and a mixed vascular and diabetic type of retinopathy. But even when all of the clinical manifestations of the Kimmelstiel-Wilson syndrome are present, the diagnosis of intercapillary glomerulosclerosis can be established with complete certainty only by microscopic examination of the kidneys.

Changes in the Ocular Fundi. The results of careful ophthalmoscopic examination of thirty-two diabetic patients in this study

who were later shown at necropsy to have intercapillary glomerulosclerosis emphasize that retinopathy is a common accompaniment of this renal lesion. When changes in the ocular fundi are present, they almost always include some features attributable to diabetes. The diabetic features may escape detection if the peripheral zone of the retina is not carefully examined. Among patients who have an advanced diabetic or mixed vascular and diabetic retinopathy the chances of its being associated with intercapillary glomerulosclerosis are great.

SUMMARY

Intercapillary glomerulosclerosis, as herein defined, was found in 19.5 per cent of 313 diabetic patients on whom necropsy examinations were performed. That the lesion is not specific for diabetes, at least morphologically, is shown by the fact that it was found in 12.3 per cent of eighty-one cases of chronic glomerulonephritis and in 5.2 per cent of 134 cases in which death was due to hypertension and its complications. Severe lesions were found only in cases of diabetes and glomerulonephritis, and were by far the most frequent in cases of diabetes. There were important differences in the clinical behavior, respectively, of cases of diabetes and those of glomerulonephritis in which intercapillary glomerulosclerosis was present.

The evidence suggests that intercapillary glomerulosclerosis is a slowly progressive process, related to the duration of the diabetes.

The diagnosis of intercapillary glomerulosclerosis cannot be established with complete certainty during life but the condition can be strongly suspected in patients who have diabetes mellitus of long standing associated with albuminuria, hypertension, renal insufficiency and mixed vascular and diabetic retinopathy. In rare instances the

condition is associated only with diabetes and albuminuria.

Retinopathy is a common accompaniment of intercapillary glomerulosclerosis. In practically all instances it includes features of diabetic retinopathy. The predominant etiologic factor in the retinopathy observed in these cases is usually not the renal disease nor the hypertension, but the diabetes. There are no retinal findings which are specifically indicative of the presence of intercapillary glomerulosclerosis; however, the more advanced types of diabetic retinopathy are more or less regularly associated with this renal lesion.

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Diabetes and Hypertension

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WHEN discussing the relationship of diabetes and arterial hypertension, the majority of authors believe that hypertension is more frequent in diabetics than in non-diabetics, the inference being that the metabolic changes of diabetes are favorable to the development of increased blood pressure. As to the effect of hypertension on diabetes, many investigators believe that circulatory changes associated with hypertension predispose to the development of diabetes through circulatory disturbances in the pancreas. Little or nothing is known of the effect of fluctuations in the severity of the diabetic condition upon the level of the blood pressure. In the following this relationship will be considered in connection with a number of cases I had occasion to observe. For the sake of simplicity and convenience, the amount of blood sugar will be taken as an indicator of the severity of the diabetic condition. In some of the cases which will be described, diabetes developed during an observation necessitated by another ailment. In others, the effect of fluctuations of the blood sugar level occurring during diabetic therapy was observed on the blood pressure. In all cases associated with hypertension a relationship between blood sugar and blood pressure was found which, in general, was inverse. In cases in which hypertension was absent there was apparently no relationship between blood pressure and blood sugar during the development of diabetes or following therapy.

CASE REPORTS

CASE I. Mrs. I. S., age thirty-four, came under observation on October 2, 1930. She

complained of irritability and restlessness. Two weeks previously high blood pressure was found by another physician. She had had mumps in childhood. Eight years ago an "ovarian tumor" had been removed. On examination nothing noteworthy was found except a blood pressure of 170/110 mm. Hg. Urine examination, blood chemistry, eyegrounds, etc., were normal.

Subsequent observations, which extended from October 2, 1930, until June 8, 1942, are summarized in Table I and Figure 1. It can be seen that following antiretention therapy¹ there was a drop and following the discontinuation of this therapy there was a rise in the blood pressure on several occasions. This relationship is not always clear, possibly either because of characteristics inherent in this case (psycho-neurosis, etc.) or because of inaccuracies in the observation of the diet. However this may be, the systolic blood pressure reached 200 mm. or more on occasions and dropped to 150 mm. or less on others. In 1936, diabetes was discovered. Several months prior to the discovery and probably at the time of the onset of diabetes, and presumably at the time of the initial increase of the blood sugar, the blood pressure began to decrease and remained below 160 mm. systolic for over a year with occasional drops to below 130 mm. The blood sugar fluctuated between 210 mg. and 220 mg. at the onset of the diabetes. Under the influence of therapy with diet and insulin it at first ranged between 114 mg. and 183 mg., but during the last two and one-half years of observation it remained constantly below 150 mg. (Following an initial glycosuria there was absence of sugar in the urine.) After the discovery of diabetes, and during the period of the drop in the blood sugar, the blood pressure remained at the previous low level for about six months. Thereafter the blood pressure began to rise, at first to moderate levels and then, year by year, to considerably increased levels. (Table I and Fig. 1.)

In this case of essential hypertension the blood pressure dropped simultaneously with the onset of diabetes and returned to the previous high level and beyond following an improvement in the diabetic metabolic state as indicated by the blood sugar.

reaching the level of 180/86 mm. (December 19, 1940). From that date on there was a gradual drop in the blood pressure with the exception of March 5, 1942, when a reading of 190/90 mm. was obtained. On March 5, 1942, diabetes was discovered with moderate glycosuria and a blood

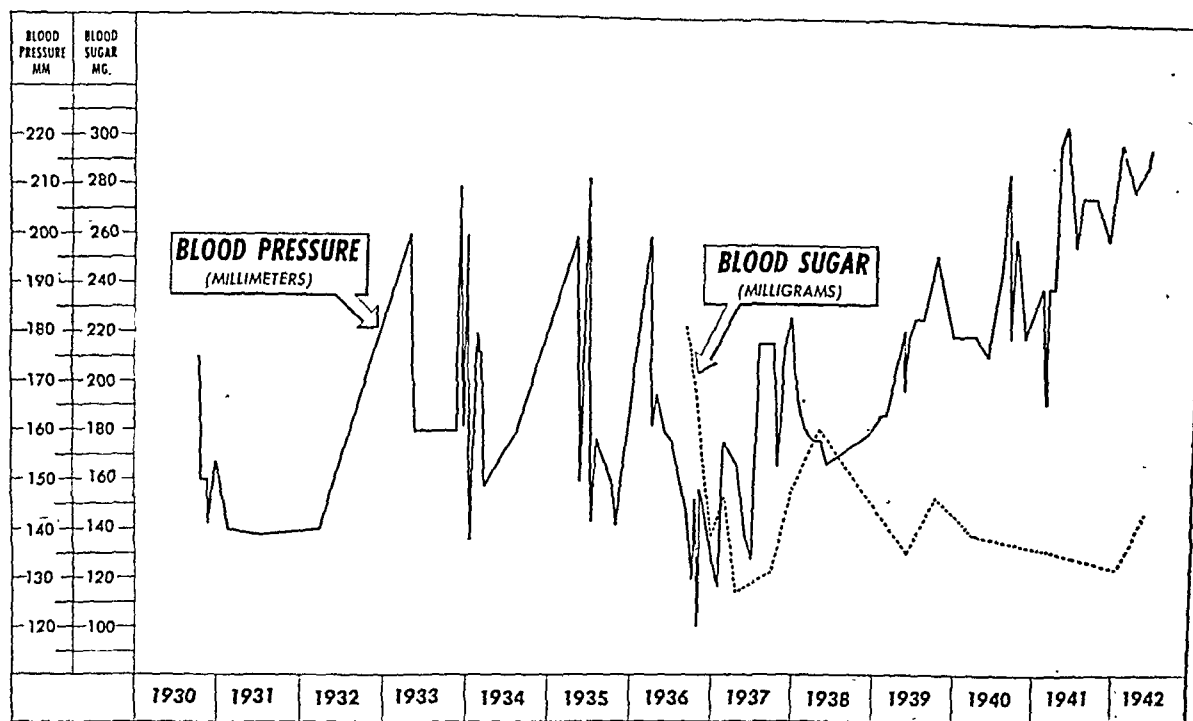


Fig. 1.

CASE II. Mrs. E. D., age sixty, came under observation August 7, 1934. In January, 1934, she had an attack of pain in the precordial region, associated with palpitation. At that time coronary occlusion was diagnosed. Two years prior to and following that attack she had a tight feeling in the chest and palpitation on effort. On examination enlargement of the left ventricle of the heart and impurity of the heart sounds were noted. There was also a mild secondary anemia. The blood pressure was 146/90 mm. The patient has been under observation to date. Mild precordial sensations were present as a rule. Until the end of 1935 the blood pressure readings were normal; they were usually below 130 mm. systolic and 80 mm. or less diastolic. (Table II, Fig. 2.) From 1936 there was a slight increase in the blood pressure, 140 mm. or 146 mm. systolic and 80 mm. or 90 mm. diastolic on most occasions. At the end of 1940 there was a further increase, the blood pressure

sugar of 348 mg. A routine urine examination in August, 1941, showed an absence of sugar, so that it may be assumed that manifest diabetes developed between that date and the date of discovery. As in Case I the drop in blood pressure in this case also preceded the discovery of diabetes and, it may be assumed, coincided with the initial increase of the blood sugar. The diabetic condition improved rapidly with the help of diet and insulin, the glycosuria disappeared and the blood sugar dropped to low normal levels, so that the administration of insulin was discontinued on June 15, 1943. (Table II.) Subsequently a moderate increase in the blood pressure developed, the measurements ranging between 138/70 and 162/84 mm.

As in Case I, in this case also the blood pressure dropped simultaneously with the onset of diabetes and gradually increased following improvement in the diabetic met-

TABLE I

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
10/2/30 ¹	170/110		4/25/35 ¹	200/120		10/6/37	154/94	
10/6/30	170/110		5/8/35	164/100		11/9/37	178/100	
10/13/30	150/90		5/10/35	160/104		12/1/37	184/100	157
10/20/30	150/104		5/12/35	150/92		12/4/37		
11/2/30	150/104		5/14/35	180/114				
11/17/30	142/96		5/16/35	150/86		1/5/38	166/100	
12/24/30	154/104		5/18/35	210/120		2/3/38	162/100	
			5/20/35	164/94		3/24/38	158/100	
2/13/31	140/90		5/22/35	180/110		4/28/38	158/100	183
6/24/31	138/80		5/24/35	212/120		5/25/38	154/100	
			5/29/35	158/94		6/28/38	184/104	
3/19/32	140/100		5/31/35	160/100		11/30/38	160/96	
4/1/32 ²	140/90		6/3/35	142/90				
			6/5/35	164/100		1/16/39	164/96	
			6/8/35	180/110		2/17/39	164/100	
4/28/33 ¹	200/110		6/11/35	182/110		5/9/39	182/106	
5/5/33	160/100		6/13/35	152/100		5/11/39	168/100	
7/24/33	160/100		6/15/35	158/96		5/24/39	180/120	131
11/9/33 ²	160/90		9/25/35	150/100		6/24/39	184/100	
11/27/33 ¹	210/120		10/19/35 ²	142/100		7/27/39	184/100	
11/28/33	190/120					9/26/39	196/110	156
12/1/33	184/90		3/18/36 ¹	200/120		12/7/39	180/100	
12/4/33	168/100		3/25/36	162/94				
12/5/33	162/100		4/6/36	168/100		1/17/40	180/100	144
12/8/33 ²	178/100		5/22/36	160/100		3/26/40	180/100	138
12/17/33	164/106		6/27/36	158/100		5/23/40	176/94	
12/19/33	176/106		8/21/36 ³	145/90	224	7/15/40	194/104	
12/23/33	176/106		8/25/36 ⁴			8/9/40	214/114	
12/26/33	200/120		9/3/36	144/90		8/29/40	180/92	
12/27/33	198/104		9/9/36	130/84		9/13/40	200/120	
12/30/33	176/104		9/17/36	130/84	214	11/6/40	180/100	
			9/23/36	146/90				
1/2/34	168/100		10/1/36	140/90		1/29/41	190/110	133
1/4/34	178/100		10/8/36	146/90		2/7/41	166/90	
1/6/34	138/100		10/15/36	120/80		2/21/41	190/100	
1/9/34	176/100		10/21/36	148/90		3/12/41	190/100	
1/11/34	164/88		11/6/36	128/70		4/8/41	220/120	
1/16/34	156/100		11/25/36	136/84		5/2/41	224/116	
1/18/34	148/96		12/9/36	134/84		6/19/41	198/110	
1/20/34	154/100		12/24/36	136/74	139	7/23/41	208/108	
1/22/34	180/106					9/12/41	208/100	
1/26/34	176/106		1/21/37	128/80		11/17/41	200/100	
1/29/34	176/104		2/16/37	158/100	154			
3/6/34	154/100		4/16/37	154/80	114	1/6/42	220/120	126
6/15/34	148/100		5/26/37	138/90		3/9/42	210/104	
8/2/34	160/100		6/21/37	134/90		5/27/42	216/110	148
			7/16/37	178/90		6/8/42	218/110	
			9/8/37	178/90	122			

¹ Antiretentional diet begun.² Antiretentional diet discontinued.³ Diabetes discovered, urinary sugar 1%.⁴ Diabetic therapy begun with diet and insulin.

abolic state as indicated by the blood sugar.

CASE III. Mrs. T. R., age sixty, began treatment on May 6, 1942. Diabetes had been present for thirteen years. The treatment consisted of diet. Cholecystectomy was performed

in the blood pressure to the previous level took place.

CASE IV. Mrs. I. P., age seventy-two, began treatment on October 13, 1942. She had had diabetes for twenty years, the treatment consisting of diet and the administration of insulin.

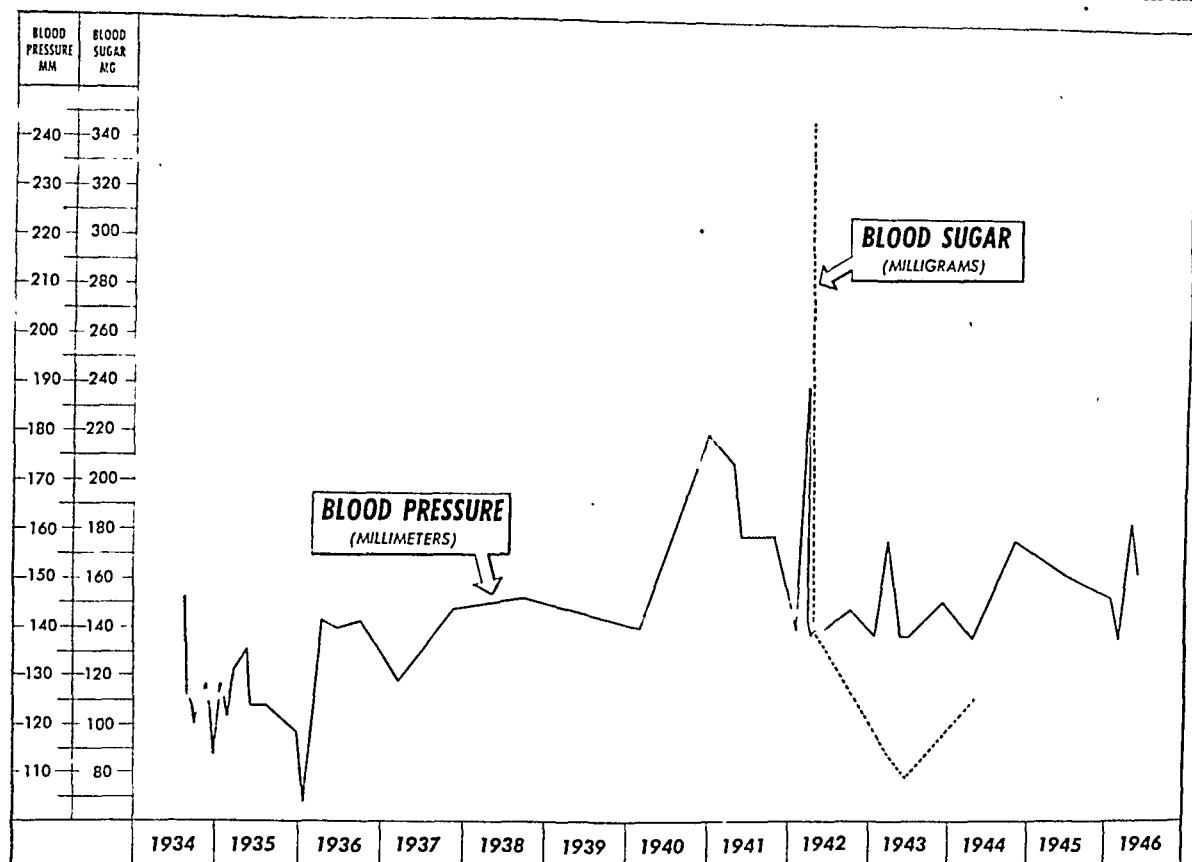


FIG. 2.

in 1927. Examination showed a left ventricular hypertrophy of the heart, dilated aorta, blood pressure 170/90 mm, urinary sugar 1 per cent, blood sugar 304 mg. On dietetic therapy glycosuria cleared up but the blood sugar rose to 354 mg. at first. Simultaneously there occurred a drop in the blood pressure to 120/80 mm. When the blood sugar subsequently dropped to between 181 and 192 mg. a gradual rise occurred in the blood pressure to 172/90 mm.

This case showed a rise in the blood sugar which was followed by a drop in the blood pressure. The drop in blood pressure persisted for a while during a period of decreased blood sugar, but then an increase

Precordial pains on effort and intermittent claudication were present for the last few months. Examination showed the following: hypertrophy of the left ventricle of the heart, left dorsalis pedis artery not palpable. Electrocardiogram: low upright T waves. Urine: 1.2 per cent sugar, blood sugar 217 mg. Following dietetic and insulin therapy there were wide fluctuations in the blood sugar level although urine examination showed absence of sugar, or the presence of traces only. The fluctuations were caused by irregularity in following dietary instructions and by frequent insulin reactions necessitating reductions in the amount of insulin administered. An initial rise in the blood sugar was followed by a considerable drop in the blood

pressure, which drop—similar to the observations in previous cases—persisted for a while in the presence of reduced blood sugar. A further drop in the blood sugar was followed by a rise in the blood pressure, while a subsequent and persistent increase in the blood sugar was associated

203 mg. The blood sugar, though fluctuating, showed a good response to therapy at first. Later there was a persistent rise caused by frequent insulin reactions which led to reduction of the quantity of insulin administered. The blood pressure was usually normal, or

TABLE II

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
8/7/34	146/90		4/4/41	174/60	
8/20/34	126/80		5/17/41	158/70	
9/4/34	124/76		8/2/41 ¹	158/70	
9/18/34	120/76		10/10/41	158/84	
10/5/34	124/70				
11/2/34	128/74		1/21/42	140/80	
11/23/34	124/76		3/5/42 ²	190/90	348
12/21/34	114/74		3/16/42	142/82	
			3/20/42	138/80	
1/18/35	128/74		4/15/42	140/80	140
2/15/35	122/74		5/28/42	140/70	
3/15/35	132/74		9/18/42	144/86	
5/3/35	126/76				
5/31/35	124/80		1/18/43	138/70	
8/8/35	124/80		3/10/43	158/80	89
11/28/35	118/70		5/13/43	138/70	
			6/15/43 ³	138/76	78
1/17/36	104/70		11/18/43	146/80	
4/3/36	142/90				
6/12/36	140/90		4/4/44	138/70	111
9/25/36	142/80		10/13/44	158/80	
3/5/37	128/80		6/7/45	152/80	
11/5/37	144/80				
			1/8/46	146/80	
9/12/38	146/84		2/15/46	138/70	
			4/9/46	162/84	
2/24/40	140/82		5/7/46	152/80	
12/14/40	180/86				

¹ Urine negative.

² Diabetes discovered, urinary sugar 3%, therapy with diet and insulin.

³ Insulin discontinued.

with a drop in the blood pressure to normal or almost normal levels. (Table iv, Fig. 4.)

CASE v. Mrs. L. D., age forty-seven, was first examined on February 27, 1939. Diabetes was discovered two years before, when diet and insulin were administered. She had frequent insulin reactions and difficulty in keeping the urine sugar-free. Physical examination revealed nothing abnormal; blood pressure 130/90 mm., urine contained 1½ per cent sugar, blood sugar

TABLE III

Date	Blood Pressure, Mm.	Blood Sugar, Mg.
5/6/42	170/90	
5/15/42	158/80	
5/22/42	140/70	
6/5/42	140/70	
6/26/42	128/80	354
7/17/42	120/80	
8/14/42	138/80	181
9/16/42	120/80	
10/16/42	150/84	190
1/15/43	162/80	192
2/24/43	172/90	

showed a slight increase, indicated by an occasional diastolic pressure of 90 mm. or 96 mm. and a single systolic blood pressure measurement of 156 mm. At best, with such low levels in the blood pressure, no clean-cut relationship can

TABLE IV

Date	Blood Pressure, Mm.	Blood Sugar, Mg.
10/13/42	200/100	217
11/6/42	180/80	250
11/13/42	190/90	195
12/4/42	170/80	
12/30/42	158/80	
1/29/43	158/80	147
3/5/43	188/100	
4/12/43	152/70	211
5/18/43	164/90	
6/8/43	166/90	214
7/23/43	166/80	
9/7/43	120/70	231
10/14/43	150/74	

be expected between the blood sugar and a measurement which is so much under the influence of emotional factors as is the blood pressure. However, as shown in Table v and Figure 5, the blood pressure was at its highest in

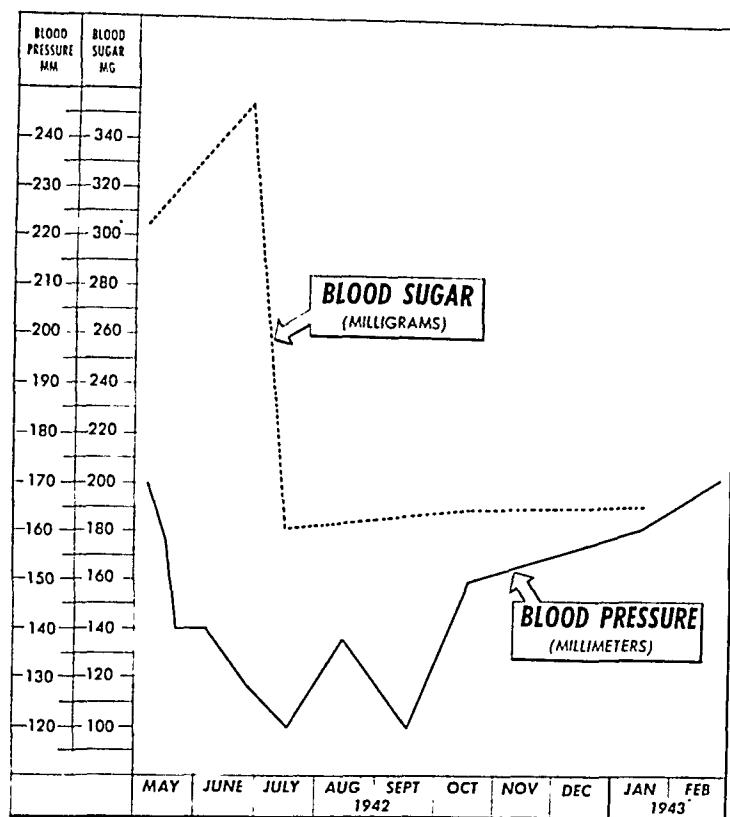


FIG. 3.

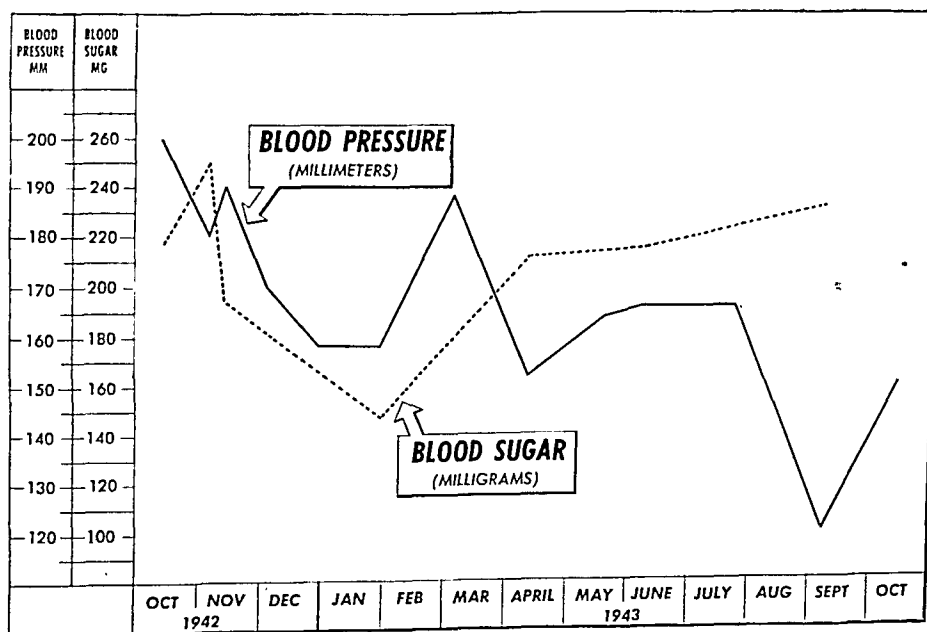


FIG. 4.

the period in which the blood sugar was at its lowest (June 20, 1939, and September 6, 1939, respectively), and a relatively sudden rise in the blood sugar was followed by a drop in the blood pressure below the "normal" level. (March 18, 1940,—see Table v and Fig. 5.) Also, most

no appreciable changes in the blood pressure in cases in which hypertension is absent. The following example will suffice as an illustration:

CASE VI. Miss W. G., age seventy, was first examined on January 2, 1941. She complained

TABLE V

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
2/27/39	130/90	203	4/5/40	128/90	
3/21/39	140/90	164	4/12/40	120/80	
4/1/39	120/80		4/30/40	126/90	
5/5/39	120/70		5/28/40	126/84	
6/20/39		143	8/3/40		220
9/6/39	156/90		9/4/30	128/90	
11/4/39	140/96	164	11/12/40	124/80	188
12/12/39	140/90				
			2/3/41	136/80	
			5/29/41	120/80	316
2/2/40	136/80	188	11/5/41		212
3/18/40	96/68	230			
3/20/40	114/70		3/14/42	132/90	
3/26/40	124/80		4/17/42		318
4/1/40	138/90		6/26/42	140/90	321

frequently, the curve of the blood pressure followed the curve of the blood sugar in reverse, as shown in Figure 5.

In none of these cases was treatment accompanied by considerable gain in weight which might have influenced the blood pressure. In fact, of the five patients four lost weight during the period of observation and the gain in weight of the fifth (Case v) was not more than 2.5 kg. The figures are as follows:

	Body Weight in Kg.				
	Case No. I	Case No. II	Case No. III	Case No. IV	Case No. v
Beginning of observation	62	75	73.5	75.5	55.5
End of observation	60	64.5	70	71.5	58

Attention has been called to the fact that development of diabetes is associated with

TABLE VI

Date	Blood Pressure, Mm.	Blood Sugar, Mg.	Date	Blood Pressure, Mm.	Blood Sugar, Mg.
1/2/41	120/60		5/13/44	124/60	
3/21/41	126/60		5/26/44	140/72	306
4/4/41	130/70		5/31/44	132/70	
5/2/41	126/60		6/6/44	126/60	225
6/3/41	126/62		6/13/44	124/60	
9/22/41	130/70		6/21/44	122/60	86
			6/28/44	114/60	
6/6/42	130/70		9/9/44	110/60	
9/23/42	120/60		9/26/44 ²	120/62	112
			10/24/44	120/64	
9/13/43	128/66		12/1/44	112/56	
1/13/44	124/62		4/11/45	110/50	111
5/5/44 ¹	110/60	280	6/12/45	100/50	

¹ Diabetes discovered, urinary sugar 2.8%, insulin therapy.

² Insulin discontinued.

of heartburn, belching, poor appetite and constipation. X-ray examination showed the presence of gallstones; the other findings were normal. The blood pressure was 120/60 mm. The patient responded satisfactorily to symptomatic treatment. In May, 1944, diabetes was discovered with a urinary sugar of 2.8 per cent and blood sugar of 280 mg. The diabetes was quickly brought under control with the aid of diet and protamin zinc insulin, so that the administration of the latter was discontinued in September, 1944. Even without the administration of insulin the urine of the patient remained sugar-free with a normal blood sugar on an unrestricted diet except for the absence of saccharose. During the entire period of observation to date the blood pressure remained normal (highest systolic blood pressure 140 mm., highest diastolic blood pressure 72 mm.) and no regularity in the relative behavior of blood sugar and blood pressure was found. (Table vi and Fig. 6.)

Similarly, fluctuations in the blood sugar in non-hypertensive diabetics were found not to be associated regularly with fluctuations of the blood pressure.

COMMENT

According to these observations, taking the level of the blood sugar as an indicator

be detectable because of the many factors which influence the blood pressure. Some of these factors other than the blood sugar level may be relatively insignificant in the presence of hypertension but sufficient to obscure the picture when the blood pressure is normal.

As to the mechanism of the relationship

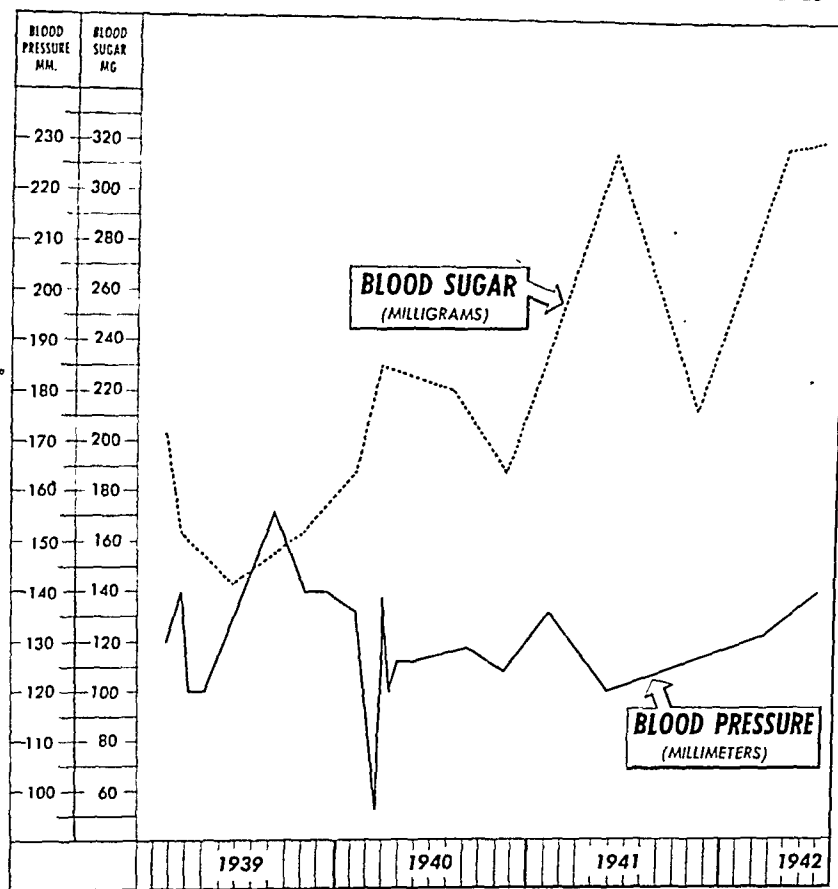


FIG. 5.

of the diabetic metabolic state, development of diabetes or impairment of the diabetic condition in the presence of hypertension, is associated with a decrease in the blood pressure. As a rule, this decrease of the blood pressure persists for a while when improvement of the diabetic condition takes place. Subsequently, if improvement of the diabetes continues, a rise in the blood pressure occurs. In the absence of hypertension no relationship between blood pressure and blood sugar is observed. The presence of such a relationship may exist, but may not

between blood sugar and blood pressure, I advanced the theory that in the pathogenesis of arterial hypertension increased blood volume, whether existing in itself or as a part of general fluid retention, is a significant factor.¹ Reduction of such fluid retention by antiretentional diet or other means is followed by significant reduction of the blood pressure in many instances.¹ This was later confirmed by a great number of unpublished observations of my own as well as by the observations of others.^{3,4,5,6} In diabetes, glucose, if eliminated in consider-

able amounts by the kidneys, acts as a powerful diuretic and leads to the well known phenomenon of polyuria (and frequently to dehydration). I had occasion to show how water retention and edema caused by certain factors are counteracted by the

This would correspond to observations made in cases in which an antiretentional diet was applied in essential hypertension, and in which the reduction in blood pressure frequently persisted for a period after the diet had been discontinued.

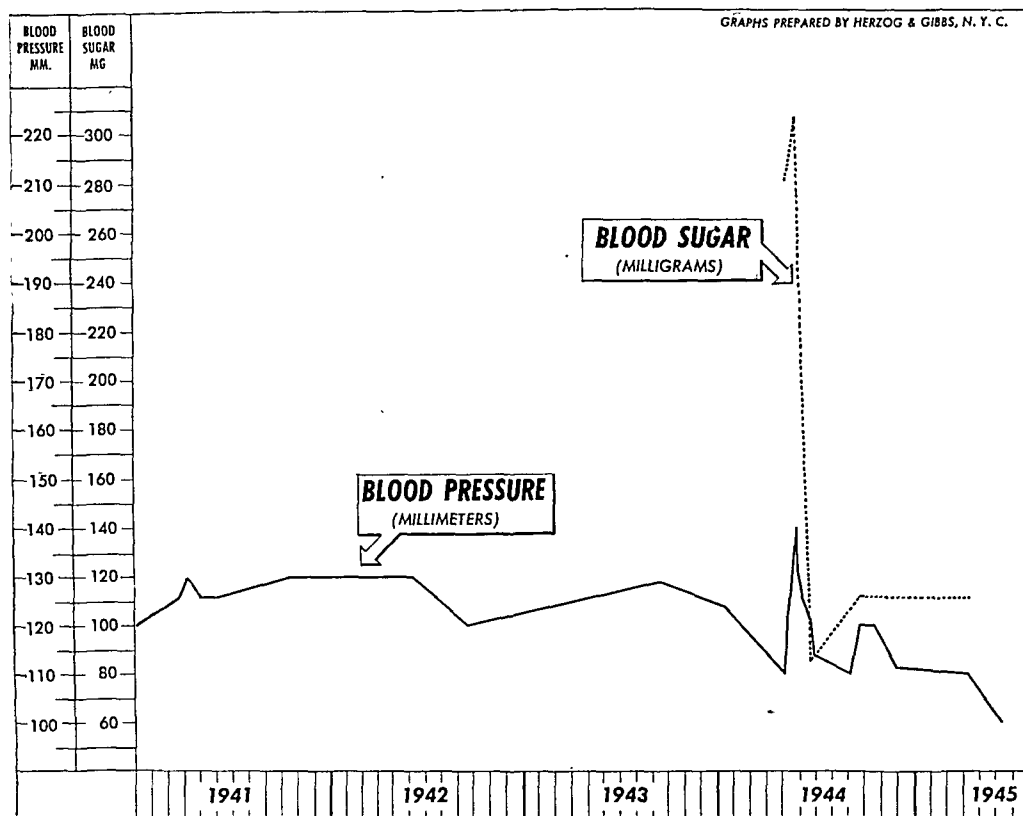


FIG. 6.

diuretic effect of eliminated glucose.² The possibility may here be considered that hyperglycemia and associated glycosuria and polyuria act as antiretentional therapy; hence the reduction of the blood pressure level. When the diabetic state improves and hyperglycemia and glycosuria decrease, retention again develops and the hypertension increases. In view of the fact that the decrease in blood pressure usually outlasts the glycosuria and hyperglycemia, it would be necessary here to assume that the dehydrating effect of the glycosuria persists for a period beyond the actual polyuria, and that considerable time is required for further retention to develop in the organism.

Other concepts of the mechanism of the effect of the fluctuations in blood sugar on the blood pressure are also admissible. In particular, involvement of the endocrine glands may be considered. It is possible that a drop in the blood sugar acts as a stimulant to those endocrine glands which influence both the blood sugar and the blood pressure in a positive direction (*vide* for instance the effect of the adrenal cortical hormone on the blood sugar and on the blood pressure). The increased output of a hormone which raises both the blood sugar and the blood pressure would thus lead to increased blood pressure; and conversely, a rise in the blood sugar would decrease stimulation of

such gland or glands, and that would then lead to diminished blood pressure.

It remains for further investigations to show which concept best corresponds to the facts.

As a practical consideration the following should be mentioned. If increased blood sugar leads to a decrease of the blood pressure, and decreased blood sugar leads to an increase of the blood pressure, the usual aim in medical practice of normalizing the blood sugar may not be to the best advantage of the hypertensive diabetic patient. It is conceivable that it might be more advantageous to standardize the blood sugar at a moderately increased level in order to keep the hypertension at a lower level.

SUMMARY

1. Cases of diabetes associated with hypertension are presented in which the effect

of fluctuations of the blood sugar level on the blood pressure was observed. In these cases an inverse relationship existed between the level of the blood sugar and that of the blood pressure.

2. No such relationship was found to exist in diabetics in the absence of hypertension.

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Insulin Mixtures

*An Evaluation of Their Use in 150 Cases**

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SHORTLY after the discovery of insulin it was found that soluble, amorphous insulin was too evanescent in its action and required the daily injection of multiple doses, especially for the satisfactory control of severe diabetics. Insulin has since undergone periodic modifications intended to make it a smoother acting preparation, one which would free the patient from hypoglycemic reactions and eliminate the necessity for multiple injections during the course of the day.

Attempts at retardation of the insulin effect were first made by Leyton.¹ He suspended solutions of insulin and of dry insulin powder in oil and in oil-emulsions. He found that there was no difference in its action. The insulin was rapidly taken up by the blood serum in all cases. The problem then was approached by preparing a precipitated compound of insulin which was sparingly soluble in the body and would thus release the insulin slowly. Gray² prepared an insulin tannate which had the property of acting longer than ordinary insulin. Jacobs and Ricketts³ succeeded in obtaining a prolonged and retarded insulin action by precipitating insulin with safranin. Rosenthal and Kamlet⁴ produced a similar effect by precipitating insulin out of solution with alum. Hagedorn et al.⁵ precipitated insulin with protamine. Hagedorn selected the monoprotoamine from the sperm of *Salmo iridens* for precipitating insulin, because the precipitate has the lowest

solubility of all the protamine insulin compounds. This proved to be the most successful compound thus far prepared.

It soon became apparent that although protamine insulin was smoother acting than unmodified insulin and eliminated the necessity for multiple injections, it possessed certain disadvantages. One of its chief defects was that too long a delay occurred in the production of an insulin effect after injection. A significant insulin effect does not become apparent for a period of six to eight hours after injection. The injection of protamine insulin before breakfast fails to provide a satisfactory insulin effect during the prandial period of the same day but produces the peak of its action in the post-prandial period. This imposes a specific disadvantage in the severe diabetic since it becomes necessary to give a dose of protamine insulin large enough to be effective the following day. Such large doses, frequently of 100 to 125 units, have the undesirable property of producing hypoglycemic reactions, especially in the early morning hours. In order to circumvent this disadvantage of protamine zinc insulin, a technic was evolved of providing the patient with a supplementary dose of unmodified insulin as a separate injection at the same time that the protamine insulin was injected. It was found that these two injections had to be administered before breakfast in order to produce the most satisfactory form of control.

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This led to a search for some form of insulin which in its action would hold an intermediary place between soluble unmodified insulin and precipitated protamine zinc insulin. One of the results of this line of investigation was the discovery of a loosely bound compound of globin and insulin.⁶ It was observed that in the duration and intensity of its action, globin insulin holds an intermediary position between soluble unmodified insulin and protamine zinc insulin. Although some of the earlier reports on the use of this agent appeared to be very favorable, our own experience revealed to us that globin insulin has a mildly retarded action, incapable of maintaining an insulin effect for twenty-four hours unless given in large doses. This proved to be a disadvantage in the severe diabetic because such patients became susceptible to severe hypoglycemic reactions six to eight hours after the administration of this agent.

An interesting series of investigations has recently been reported describing the results of mixing unmodified insulin with protamine insulin. This technic originated with Graham⁷ who found that mixing the insulins gave a preparation which possessed some of the characteristics of both quick-acting unmodified insulin and long-acting protamine insulin. Ulrich⁸ later pointed out that if a sufficiently large amount of unmodified insulin is added to protamine insulin a point is reached beyond which unmodified insulin remains intact in the mixture. The first important practical contributions which made mixtures clinically feasible were those of Colwell et al.⁹ and Peck.¹⁰ They showed that when soluble insulin is added to protamine insulin in the proportion of two or three parts soluble insulin to one part protamine insulin, intermediate effects are obtained without influencing the prolonged action of protamine insulin.

In December, 1943, we decided to insti-

tute the use of insulin mixtures in a series of diabetics under our observation. Since then we have accumulated experience with one hundred fifty patients. Primarily we followed the technics of the previous investigators in this field, but quickly found that employing mixtures of two parts unmodified insulin to one of protamine, or three parts of unmodified insulin to one of protamine, did not achieve the goal of adequately controlling all the diabetics. We found that the use of one or even two fixed ratios was not suitable in all cases. In our series the required range of ratios of mixtures was between one part soluble insulin to one part protamine insulin, and five parts soluble insulin to one part protamine insulin. In no case did we find it necessary to give a ratio of less than 1:1.

Mixtures were prepared by the patients who mixed each dose in the insulin syringe at the time of administration. This was done according to the following directions which were given to the patients:

DIRECTIONS FOR USING INSULIN-MIXTURE

1. Draw up air to the _____ mark.
2. Inject the air into the regular insulin bottle and withdraw insulin to the _____ mark. Then withdraw needle from insulin bottle.
3. Hold syringe upside down. Draw air into syringe till piston reaches _____ mark.
4. Shake protamine insulin bottle vigorously.
5. Insert needle in the bottle of protamine insulin and inject the *air only* into the bottle. Withdraw protamine insulin to the _____ mark.
6. Draw in air bubble into syringe and mix.
7. Turn syringe upside down and expel bubble.

8. You are now ready to administer the insulin mixture.

No patient was permitted self-administration of insulin mixtures until we were convinced that he had mastered the technic.

RESULTS

We considered a patient satisfactorily transferred to insulin mixtures when glycosuria was minimal, the blood sugar as close to normal as possible and the patient was maintained in a satisfactory nutritional state, felt clinically well and was free from hypoglycemic reactions. The results reported are based upon observations made in 150 cases over a period of two years. Figure 1 presents a graphic summary of all the cases studied, showing the distribution of the ratios of unmodified to protamine insulin employed in the mixtures. It will be seen that fifteen cases were satisfactorily controlled on a mixture of one part soluble insulin to one part protamine insulin; twenty-one patients on $1\frac{1}{2}$ parts soluble insulin to 1 part protamine insulin; seventy-nine patients took a mixture of 2 parts soluble insulin to 1 part protamine insulin; fifteen patients took $2\frac{1}{2}$ parts soluble insulin to 1 part protamine insulin; fourteen took 3:1; and four took 5:1 of soluble insulin to protamine insulin.

It will be seen that only 53 per cent of all cases were satisfactorily maintained with a mixture of 2 parts soluble insulin to 1 part protamine insulin. We attempted to analyze these cases for the purpose of finding some equation or formula by means of which one could predict the proportion of mixtures necessary to maintain each patient. In Figure 2 is seen a breakdown of the cases showing the mixtures employed in patients, compared with their previous management when they received separate injections of soluble insulin and protamine insulin. There does not appear to be any relationship which would help us to predict the require-

ment of insulin mixtures based upon previous separately injected doses. It still appears that regardless of the ratio of separately injected doses previously administered, the majority of the patients receiving mixtures found it necessary to take a 2 to 1 proportion of soluble insulin to protamine insulin.

The question then arose as to whether there was any relationship between the severity of the disease and the ratio of mixtures necessary to control the diabetes. Figure 3 is a composite-curve showing the range of ratios employed in relatively mild diabetics and in severe diabetics. The total insulin requirement of the day was used as an index to the severity of the disease. This was considered permissible since all the patients were given high carbohydrate diets. Those taking less than 40 units per day were arbitrarily classified as relatively mild diabetics, and those taking more than 70 units per day as severe diabetics. It will be seen from Figure 3 that irrespective of the mildness or severity of the disease, the great majority of patients taking mixtures were best controlled with a proportion of 2 parts of soluble insulin to one part protamine insulin. The pattern of the curve is similar to the curve for all cases as seen in Figure 1.

It would thus appear that no factor in the previous management of the patient serves as a reliable index or criterion for predicting the proportion of soluble insulin to protamine insulin to be employed in mixtures.

Besides the statistical analysis of the cases just presented, the following are pertinent observations made regarding the clinical results with patients transferred to mixtures.

In the first place, it was observed that the frequency of hypoglycemic reactions was reduced. It was also observed that a shift in the peak of intensity of insulin activity occurred when the patients were transferred from separately injected doses to insulin mixtures. The sharpness of the action of unmodified insulin when given as a separate

injection supplementary to the protamine insulin in the morning before breakfast generally creates a tendency for reactions to occur (if they do occur) four hours after the injection. With this technic, therefore,

reaction consists in the provision of a supplementary intercibal feeding two hours after breakfast, with the patient taking lunch within four hours after taking insulin.

The use of insulin mixtures appears to

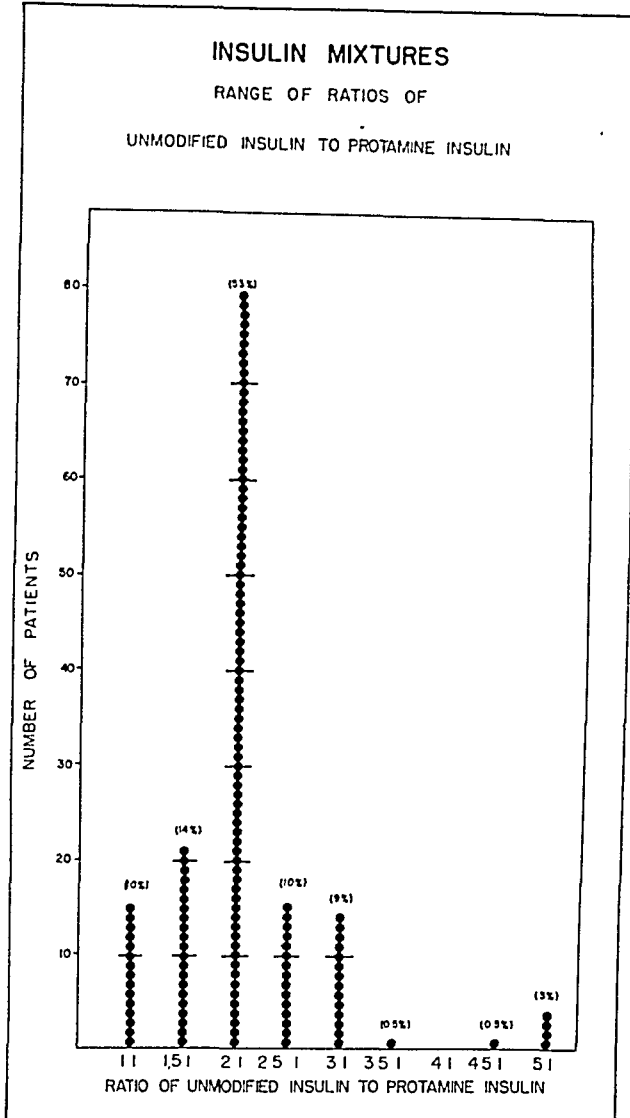


FIG. 1. Graphic summary of 150 diabetics treated with insulin mixtures. Note that 53 per cent of all the patients were successfully treated with a mixture of two parts unmodified to one part protamine insulin. The balance required mixtures ranging between 1:1 and 5:1 of unmodified to protamine insulin.

patients are susceptible to hypoglycemic symptoms before lunch when the insulin is administered in the morning before breakfast. Of course, a satisfactory practical procedure to circumvent the hypoglycemic

obviate the sharpness of action of unmodified insulin, and what is left as soluble insulin seems to serve as an intermediate-acting insulin apparently producing a peak of activity six to eight hours after injection.

It was observed that patients who take mixtures are susceptible to reactions six to eight hours after the injection. This means that hypoglycemic symptoms, if they occur, develop in the late afternoon when the patient takes mixtures in the morning before

injected doses of insulin. Most patients also reported a better sense of general well-being. In the case of one juvenile diabetic, the mother noticed that the behavior of the child appeared more normal. Weight gain has been more consistent, especially in some

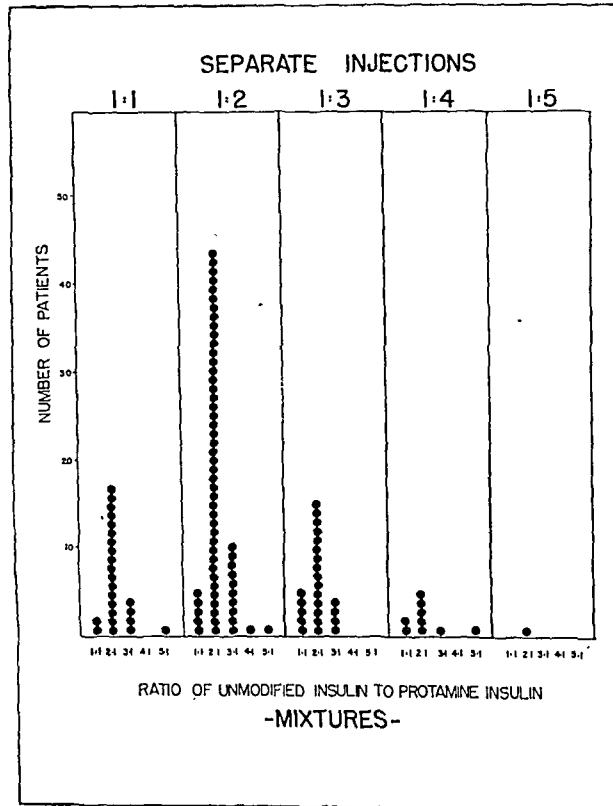


FIG. 2. This graph reveals the ratio of unmodified insulin to protamine insulin required in a mixture for patients who had previously received separately injected doses of unmodified and protamine insulin. It will be seen that regardless of the previous ratios of separately injected doses, the majority of the patients in each group required a ratio of two parts unmodified to one part protamine insulin in the mixture.

breakfast. In order to circumvent this, it was found necessary to provide a supplementary feeding six hours after the administration of the insulin mixtures.

It was found also that patients prefer the use of mixtures because one injection is eliminated. This appears to be one of the chief advantages in most of the patients previously best maintained with separately

juvenile diabetics.

In contrast to these apparent advantages, there appeared to be certain disadvantages in the use of insulin mixtures. One of the chief disadvantages of insulin mixtures is that their action is less predictable than that either of unmodified insulin or protamine insulin when given alone or as separately injected doses in the morning be-

fore breakfast. Insulin mixtures appear to be easily inactivated by infection. This becomes quickly apparent in the severe diabetic who experiences an acute upper respiratory tract infection. The patient may be evenly controlled and well stabilized

injection of the mixture. Carelessness on the part of the patient in missing the supplementary feeding in the afternoon, or even in being late for the feeding, makes him susceptible to hypoglycemic reactions.

The introduction of insulin mixtures has

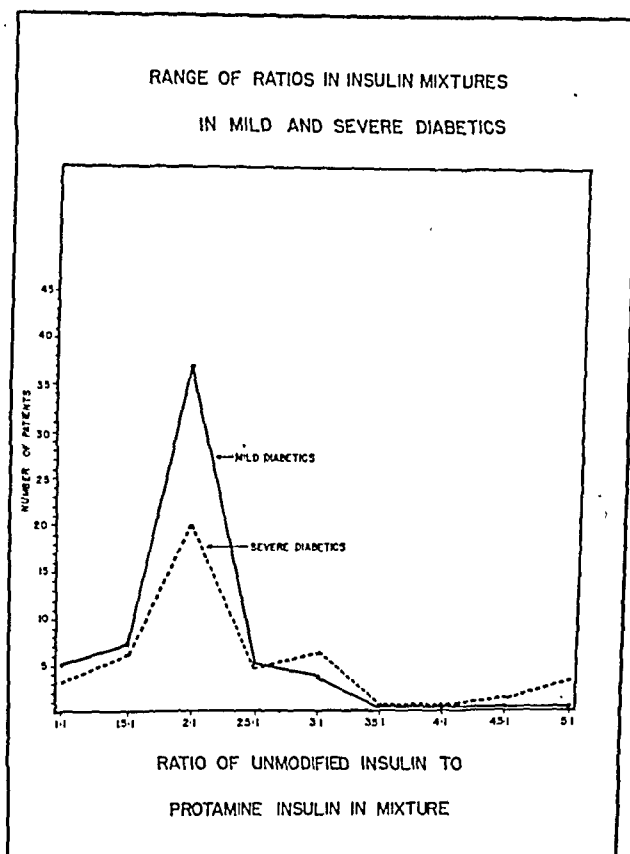


FIG. 3. Range of ratios of insulin mixtures employed in mild and severe cases of diabetes. Note that the curves run almost parallel indicating that the severity of the disease did not predetermine the ratio of the mixture.

with a specific dose of a mixture but within twenty-four hours of the onset of an infection will show a severe break in carbohydrate tolerance even though he maintains the same regularity of treatment. Another important disadvantage in the use of insulin mixtures is the necessity for closer attention to the details of dietary management by the patient and to follow-up care by the physician. The lack of predictability of the action of mixtures makes necessary meticulous care in timing the feeding after

also added a complicating difficulty to the physician's practice. A patient cannot be managed satisfactorily on insulin mixtures unless adequate information is obtained on the intensity and duration of effect of insulin mixtures in the course of the twenty-four-hour cycle. This requires an analysis of fractionally excreted specimens of urine voided over twenty-four hours, in addition to an examination of the fasting blood sugar. Besides this, the carbohydrate, protein and fat value of all foods taken in each meal and

the supplementary feedings between meals on the day that the urines are collected should be calculated.

Another important disadvantage in the use of insulin mixtures is that the patient must manufacture his own dose every time he takes his injection. Our experience indicates that any attempt to simplify the use of insulin mixtures by having pre-mixed insulin on the market, prepared by the manufacturer, physician or patient, is not the most satisfactory method of employing mixtures. Although we have found that 53 per cent of our patients are satisfactorily maintained with mixtures averaging 2 parts soluble insulin to 1 part protamine insulin, there still exists the large group of 47 per cent of patients who require mixtures in different ratios ranging from 1:1 to 5:1 of unmodified to protamine insulin. The introduction of pre-mixed insulins in such wide ratios would only tend to confuse a situation already complicated by the varieties of insulin available to the patient.

Although the statistical study in Figure 1 indicates that 53 per cent of the patients are satisfactorily maintained on a 2:1 mixture of soluble to protamine insulin, it must be stated at this point that this is only an average figure. For example, a patient who uses 55 units of unmodified insulin and 30 units of protamine insulin is classified as one taking a 2:1 mixture. Similarly, a patient receiving 70 units of unmodified insulin and 30 units of protamine insulin is also classified as taking a 2:1 mixture. The wide disparity of these two mixtures is easily seen and yet in classifying patients for average computations, the details of such mixtures are lost. A detailed breakdown of our cases indicates that the number of patients receiving an exactly 2:1 mixture represents only 20 per cent of the entire series. This again indicates that satisfactory control of the diabetes can be effected only if the patient prepares each dose.

The follow-up visit furnishes the physician with information which enables him to modify the particular ratio which the patient is receiving. Thus, the character of the prandial glycosuria, as obtained from fractional urine studies, serves as an index for establishing the dose of unmodified insulin in the mixture; while the fasting blood sugar serves as a guide to the dose of protamine insulin in the mixture. It has been our experience that while a patient may be started with a mixture in the exact proportions of 2:1, information gained from the follow-up visit might result in satisfactory control with only slight alteration of the ratio.

CASE REPORTS

CASE I. A. J., male, fifty-two years of age, has been a diabetic for the past four and one-half years. He was treated with a maintenance diet and separately injected doses of unmodified and protamine insulin up to October 6, 1944. From then on he was shifted to insulin mixtures. The diet has remained fairly constant throughout the period of observation, with an average intake of 200 Gm. of carbohydrate, 80 Gm. of protein and 125 Gm. of fat. His weight for two years before mixtures fluctuated between 134 and 144 pounds. After institution of insulin mixtures, his weight increased to an average of 150 pounds. He has experienced no reactions either on separately injected doses or on mixtures. He feels generally better since his weight increased. A graphic summary of his case for one year on separately injected doses and one year on insulin mixtures is seen in Figure 4. It will be observed that the prandial glycosuria appears to be less with insulin mixtures and the fasting blood sugars have been more frequently normal. It will also be observed that the total insulin requirements are approximately the same. The ratio of unmodified to protamine insulin in the mixtures has fluctuated between 1 to 1 and 1:5 to 1.

CASE II. T. M., a nineteen year old male, developed diabetes when he was twelve years of age and has been under our observation since

the onset. His carbohydrate tolerance has been relatively constant during the past five years during which time his total insulin requirements have averaged approximately 60 units per day. His dietary intake has also been relatively constant averaging approximately 275 to 300 Gm.

tensity of the glycosuria. His weight has remained constant throughout. He has experienced occasional mild insulin reactions under both regimens. His reactions occurred in the morning before breakfast on separate injections. He experienced occasional reactions in the late

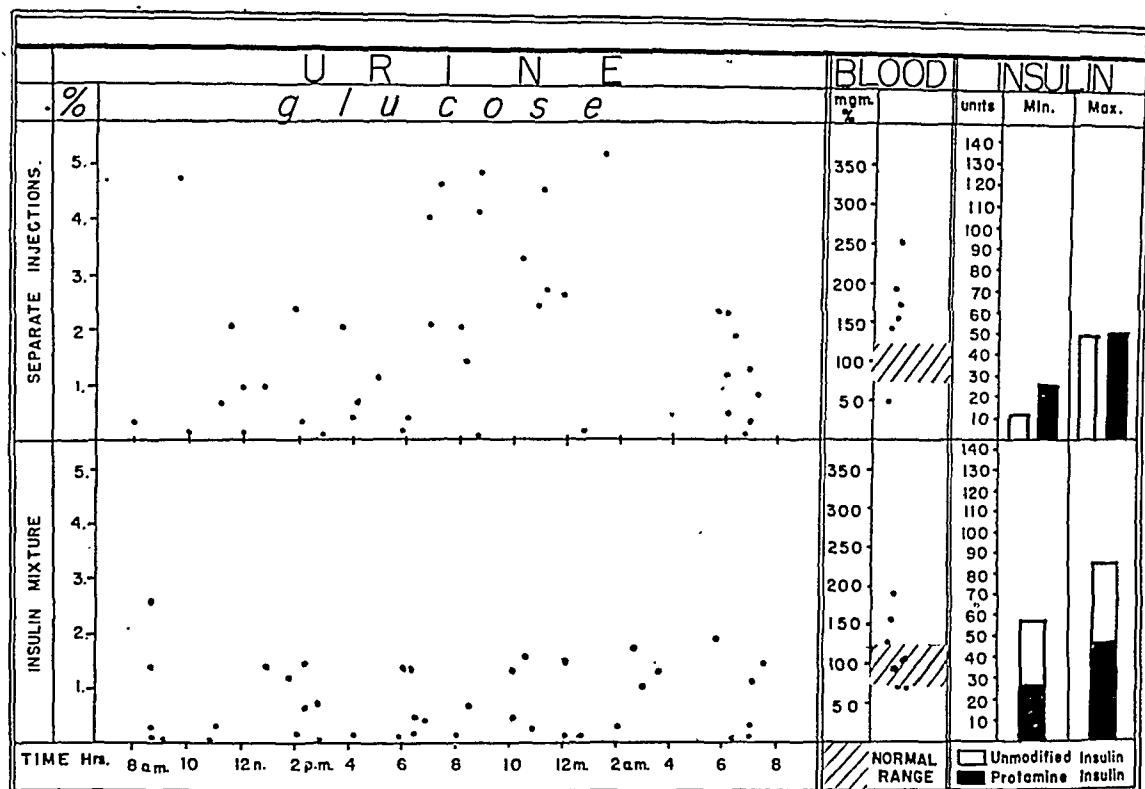


FIG. 4. Graphic summary of a fifty-two year old male diabetic (Case I in the text), comparing one year of treatment with separately injected doses of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the total insulin requirements are approximately the same, the fasting blood sugars are more frequently normal on mixtures and the glycosuria is less intense on mixtures, especially in the afternoon.

of carbohydrate, 100 to 120 Gm. of protein and 100 to 125 Gm. of fat. On April 5, 1944, he was transferred from separate injections of regular insulin and protamine insulin to insulin mixtures. Figure 5 is a graphic summary of this patient's status for one year before and one year after the institution of mixtures. His general physical condition has remained good and there have been no serious complications. His total insulin requirements are approximately the same on both regimens. It will be seen that the fasting blood sugar on treatment with mixtures is closer to the normal range but there has been practically no change in the character or in-

afternoon on mixtures. In every case these reactions occurred when the patient was late for his intercibal supplementary feedings. He was best maintained on a mixture of 2 parts regular and 1 part protamine insulin.

CASE III. F. K. is a twenty-one year old female who has been diabetic since she was eleven years of age and has been under our observation since she was sixteen. She is a severe diabetic and has been maintained in a state of well-being on a diet averaging 225 Gm. of carbohydrate, 100 Gm. of protein and 100 Gm. of fat. The severity of her diabetes is indicated by total daily insulin requirements

between 110 and 140 units per day. Her most constant dose of insulin, when given as separate injections, has been 40 units of regular insulin and 80 units of protamine insulin before breakfast. She was transferred to insulin mixtures on December 8, 1943. Figure 6 is a graphic sum-

severe diabetic and has been clinically well on a diet averaging 300 Gm. of carbohydrate, 120 Gm. of protein, and 100 Gm. of fat. He is five feet ten inches tall and his average weight was approximately 160 pounds. His maintenance insulin dose averaged 20 units of regular insulin

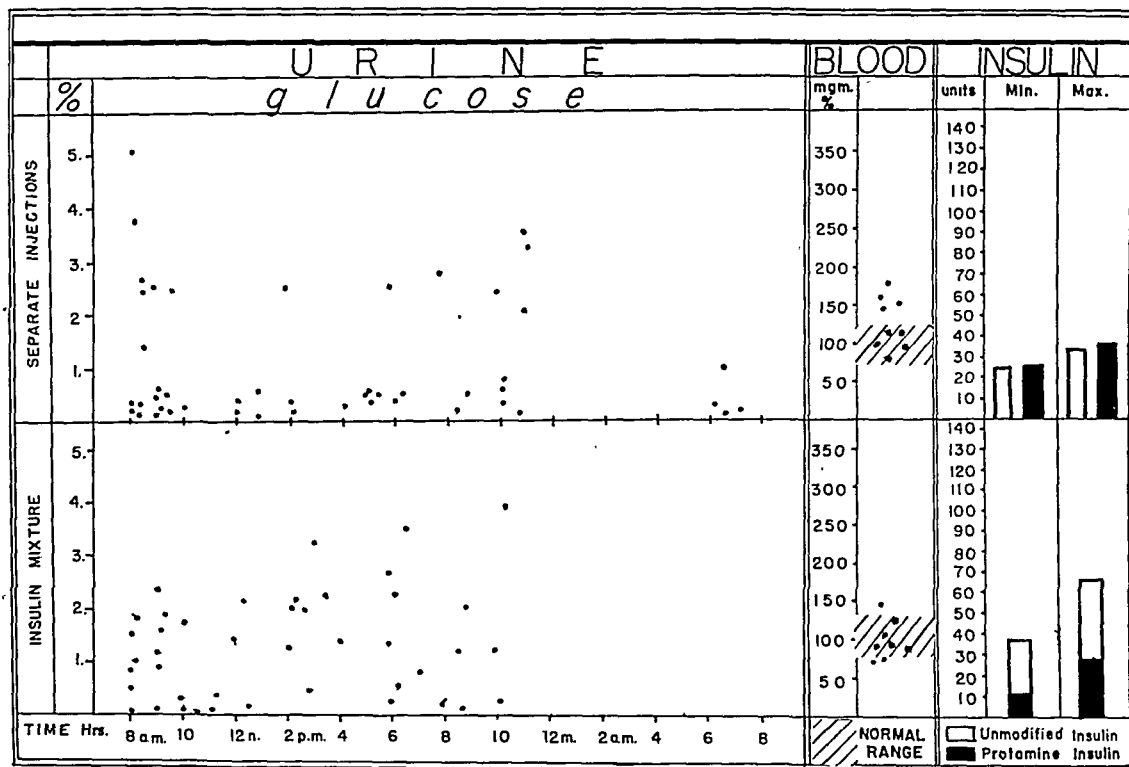


FIG. 5. Graphic summary of a nineteen year old male diabetic (Case II in the text), comparing the laboratory status for one year on separate injections of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the blood sugars are more frequently normal on insulin mixtures but that there has been no change in the intensity of the glycosuria.

mary of one year's observation on separate injections and one year on mixtures. It will be seen that the only significant change that occurred was a marked reduction in the prandial glycosuria from 4:00 P.M. to midnight. The fasting blood sugars have remained roughly at the same level but her total insulin requirements have dropped to an average of 104 units per day and she appears to be satisfactorily controlled with a mixture of 80 units of regular insulin and 24 units of protamine insulin. This is a ratio of 4:1.

CASE IV. M. R. is a twenty-one year old male who has been diabetic since the age of sixteen and came under our observation one year after the onset of his diabetes. He is a

and 60 units of protamine insulin when given as separate injections. He was transferred to mixtures on December 20, 1943. It will be seen in Figure 7 that there occurred a marked reduction in the prandial glycosuria, which appeared to be especially significant after 2:00 P.M. The fasting blood sugars have been about the same on both regimens. His average maintenance dose on mixtures has been 88 units daily, consisting of 64 units of regular insulin and 24 units of protamine insulin. This is a ratio of almost 3:1. The only additional difference in his condition is that he has gained twelve pounds since he has been on mixtures. He has experienced many more insulin reactions since he has been on mixtures than on

separately injected doses and the reactions have occurred in the afternoon between 3 and 6 P.M. The patient claims a better sense of well being on mixtures and, in spite of the greater frequency of reactions, prefers to continue on this mode of treatment because it saves an injection and because he feels better.

performed on April 2, 1944, gave a typical diabetic curve. On April 23, 1944, the patient was transferred to insulin mixtures. His fasting blood sugars have continued to be normal. His glycosuria has improved markedly so that he is either sugar-free or excreting traces of sugar in the urine. It is interesting that the dose

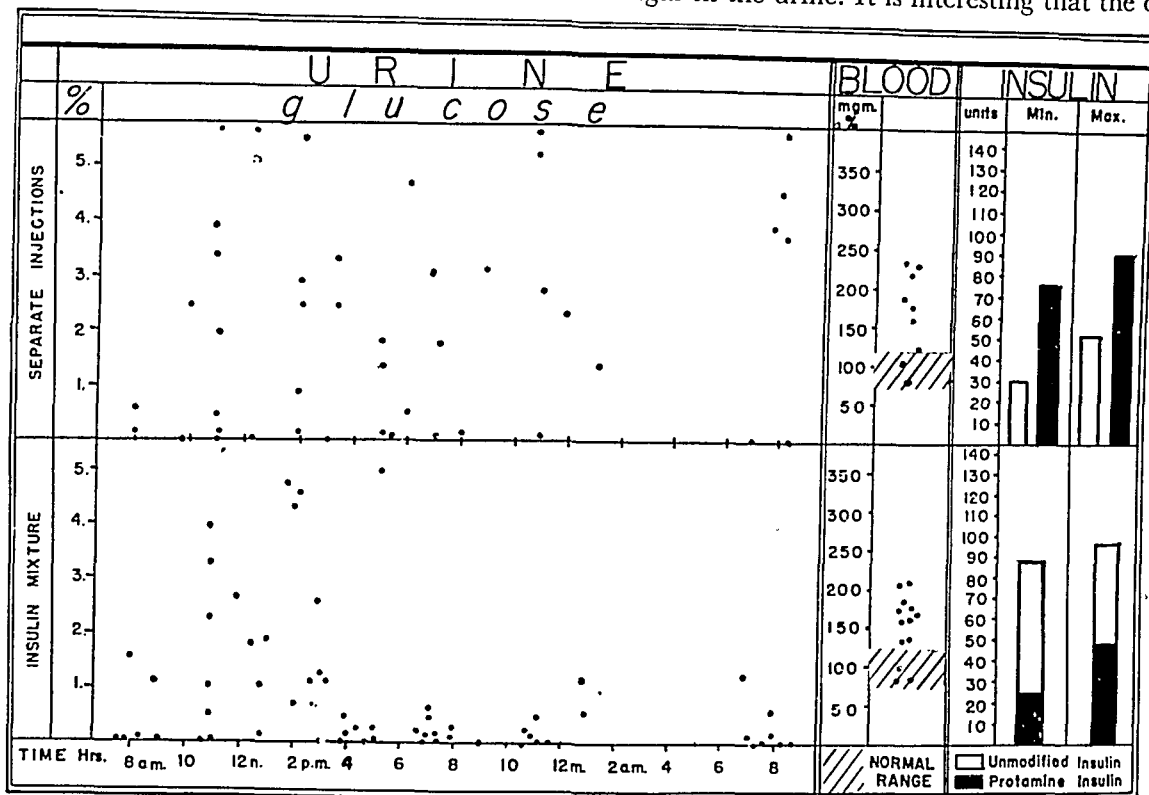


FIG. 6. Graphic summary of a twenty-one year old female diabetic (Case III in the text), comparing one year of treatment with separately injected doses of unmodified and protamine insulin with one year on insulin mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that there was a marked reduction in prandial glycosuria from 4 P.M. to midnight on insulin mixtures. The fasting blood sugars under both conditions were approximately the same. Note also that there has been some reduction in the total insulin dose on mixtures.

CASE V. I. H. is an unusual case and is one of the few patients under observation in whom the insulin dose when given by separate injections required, for satisfactory maintenance, the administration of a larger dose of unmodified insulin than of protamine insulin. This became obvious as a result of the fact that he had almost continuous glycosuria while the blood sugar remained normal even when he received 40 units of unmodified insulin and 25 units of protamine insulin by separate injections. Some doubt even developed whether this patient was a diabetic in spite of the history of the onset of the disease with classic symptoms. A glucose tolerance test

of insulin mixtures necessary to maintain this patient satisfactorily has consisted of 60 units of regular insulin mixed with 12 units of protamine insulin, a ratio of 5:1. Any attempt to reduce this ratio has always resulted in significant glycosuria. Although the patient has been clinically well on both regimens, he has gained fifteen pounds in weight since he was placed on mixtures.

It may be said that the diabetic whose total daily insulin requirement is less than 30 units per day is no problem in management with almost any type of insulin avail-

able. The intelligent use of a physiological diet with spaced intercibal supplementary feedings will result in satisfactory control of the mild diabetic whether a single dose of protamine insulin or globin insulin is employed in the morning, or whether unmodi-

to secure an insulin effect of even intensity over as much of the twenty-four hour period as possible. Although insulin mixtures are capable of accomplishing this best, the difficulty with insulin mixtures lies in their instability. As has already been indicated,

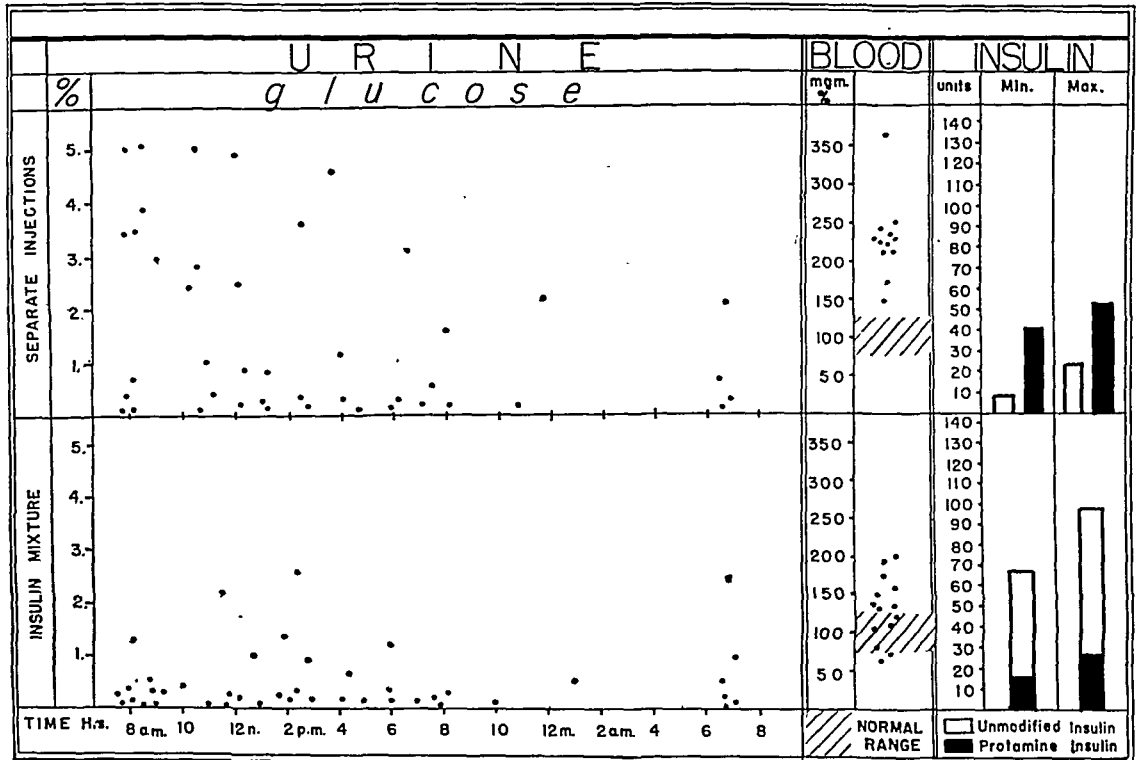


FIG. 7. Graphic summary of a twenty-one year old male diabetic (Case iv in the text) comparing one year of treatment with separately injected doses of unmodified and protamine insulin and one year on mixtures. The upper half of the chart is a record of the period on separate injections, the lower half on insulin mixtures. Note that the prandial glycosuria is less marked, especially after 2 P.M., on insulin mixtures. Note also that the fasting blood sugars are roughly the same under both conditions.

fied insulin is used in divided doses. In such cases, however, we find the use of insulin mixtures to be ideal, for the patient is best controlled by this technic.

It is the severe diabetic who presents a significant problem and in whom no satisfactory answer has as yet been obtained, even with the use of insulin mixtures.

It would appear that the use of insulin mixtures is a more desirable method of treatment in the severe diabetic than is any other previously employed technic. The important problem in the severe diabetic is

the efficiency of the insulin mixture is quickly upset in the presence of any mild infection. Those who are subject to mild respiratory infections, for example, are subject to wide fluctuations in carbohydrate tolerance. Thus, the ability to maintain a patient in a zone of satisfactory clinical control, allowing him to excrete a minimal quantity of dextrose and to maintain his fasting blood sugar close to the normal level, at the same time keeping him free from hypoglycemic reactions, can be accomplished sometimes only with much difficulty.

In this series of 150 cases, we were compelled to terminate the use of insulin mixtures in four cases because these patients experienced too many insulin reactions and could not be satisfactorily controlled.

We found it necessary also to interrupt, temporarily, the use of insulin mixtures in diabetics who became pregnant. The progressive alteration in carbohydrate tolerance with advancing pregnancy is such as to make the use of insulin mixtures undesirable. These patients have been better controlled with the use of separately injected doses of unmodified and protamine insulin during the period of gestation, allowing to return to insulin mixtures one month after childbirth. Similarly, it has often become necessary to interrupt the use of insulin mixtures in patients with severe infections and to revert to separately injected insulins until subsidence of the infection.

CONCLUSIONS

An analysis is presented of the use of insulin mixtures in the treatment of 150 diabetics observed over a period of two years.

The advantages and disadvantages of this method are discussed.

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Experience with Insulin Mixtures*

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HAGEDORN announced his work with insulin modified by the addition of protamine in 1935. His first American publication appeared in January, 1936.¹ Following considerable further modification of the original formula, this insulin was approved as protamine zinc insulin for commercial distribution and became available in this form in January, 1937.

Clinical use of this insulin showed that it had many advantages. The most important of these were that the insulin effect persisted for twenty-four hours or longer after a single injection and that continuous insulin influence was maintained. But it had shortcomings. The degree of insulin effect varied at different times during the twenty-four-hour period. There was the minor effect during the first few hours following injection and failure to control the post-prandial rise of blood sugar in a considerable number of diabetics. This latter weakness particularly was manifested in that group of patients with a total insulin requirement greater than 30 to 40 units per twenty-four hours.

As a result of these shortcomings a search for further modification of the formula of standard protamine zinc insulin became inevitable. Many such modifications have been given a trial; a number of these have been listed, with the modified formulas, in publications by Peck² over the past four years. Until the present time no modification of the formula of standard protamine zinc insulin has been evolved which excelled sufficiently in controlling hyperglycemia to justify endorsement by the Toronto Insulin Committee. Thus, no modification or re-

placement of current standard protamine zinc insulin has been approved.

Since the timing effect of the action of any insulin is dependent upon the pharmacological formula, it is evident that change of the formula will alter this particular feature of the action. Hagedorn suggested this at the time of his original announcement. Since no change in the standard formula of protamine zinc insulin has been acceptable to those charged with the responsibility of approving types of insulin, it was natural that alteration of the timing effect be attempted by clinicians by new methods of use of the commercially available insulins. As early as 1938,³ reports began to appear in the literature concerning these efforts as they pertained to mixtures of quick-acting and slow-acting insulin.

Since this is a report of clinical experience with mixtures of insulin, the authors will not enter into the discussion regarding the pharmacological changes which occur when solutions of zinc insulin crystals and standard protamine zinc insulin are thoroughly mixed. These changes have been discussed extensively by Peck,² Colwell,⁴ MacBryde⁵ and others. However, it is evident from the formulas of these two insulins (Table 1) that when a mixture is made the chemical proportions and the pH change, resulting in an alteration in the pharmacological effect. It is also obvious that these changes vary, dependent upon the proportions of the mixture.

This study differs in some respects from most of those previously reported. Our observations were made almost entirely

* From The Mason Clinic, Virginia Mason Hospital, Seattle, Washington.

upon patients seen in office practice. None were under prolonged observation in the hospital. Patients were chosen for mixtures, without selection, from those who required both quick-acting insulin and slow-acting insulin to obtain satisfactory control during

TABLE I

Insulin	pH	Zinc Mg./100 Units	Protamine Mg./100 Units
Crystalline.....	3.0	0.02	0
Protamine zinc.....	7.2	0.2	1.25
Crystalline Protamine zinc 2:1.....	5.9	0.67	0.42

the waking as well as during the sleeping hours. Practically all patients required insulin in excess of 30 units. (Table II.) Of course, only patients sufficiently intelligent to understand the technic of making mixtures were allowed to use them. In mixing,

TABLE II

Type of Diabetes	Total No. Patients	Average Total Insulin per Day Units
Juvenile..	72	53
Adult....	156	46

insulins of the same strength and of the same manufacturer were always employed.*

METHOD

When control as nearly satisfactory as deemed possible had been established on certain doses of crystalline insulin and protamine zinc insulin, the use of a syringe mixture was started. The decision as to whether to use a 1:1, a 3:2 or 2:1 proportion (the first numeral indicating crystalline insulin and the last numeral protamine zinc insulin) depended upon the number of units of crystalline and the number of units of

protamine zinc insulin employed as separate injections. If the ratio of crystalline insulin to protamine zinc insulin was low, a 1:1 mixture was employed at first and, if higher, a 3:2 or 2:1 mixture was employed. In only rare instances was a greater proportion than 2:1 used in a mixture. In a considerable number of patients studied, mixtures were necessarily changed from 1:1 to 3:2 or to 2:1 but the greatest proportion of the group ultimately used a 2:1 mixture.

After changing to a mixture the patient was observed in the office in seven to ten days. A record of urine tests at home, made before breakfast and before supper on urine which represented a bladder collection from thirty to forty-five minutes, was reviewed. The patient was then interrogated regarding reactions and subjective sense of well being. A blood sugar determination was then made two and one-half to three hours after either breakfast or the noon meal. If the findings approached the satisfactory criteria of control, no change was made in the proportions of the mixture. If night control was not satisfactory, the protamine zinc insulin effect was increased either by a change of proportion in the mixture being used, or by increase of the total number of units per dose of mixture until the night time control was satisfactory. If night time control was satisfactory and day time control was not, the proportion of crystalline insulin in the mixture was increased. If both day and night controls were unsatisfactory, the total dose of the mixture was increased or decreased, with or without a change of proportion, depending upon the indication. In order to permit any given regimen to stabilize, changes were made in the proportion of the mixture or total dosage at infrequent intervals.

The metabolic load was distributed in three equal meals and a bedtime feeding, except in children under twelve years of age to whom a mid-afternoon feeding was also

* Material for the study was supplied by Eli Lilly Company.

given. In a few younger children, a mid-morning feeding was arranged, especially if breakfast was early and lunch did not come until noon.

Diets prescribed were arranged according to our usual custom and represented the basal requirements for age, height and ideal weight plus 25 to 30 per cent, except in children to whom 1,000 calories for the first year plus 100 calories for each additional year were allowed. During adolescence the total calories were 2,200 to 2,300. The ratio of Gm. of carbohydrate to Gm. of fat most often was 2:1, and all diets were liberal in protein. Carbohydrate ranged from 165 Gm. to 180 Gm. and rarely exceeded 200 Gm. except for hard labor or during convalescence. Fat was raised or lowered in accordance with the weight curve.

CRITERIA OF CONTROL

The criteria of satisfactory control were as follows: (1) sugar-free or nearly sugar-free tests of urine accumulated in the bladder thirty to forty-five minutes before breakfast and before supper; (2) blood sugar levels of 100 to 140 mg. per 100 cc. before the noon meal, or not exceeding 200 mg. per 100 cc. two hours after the noon meal.

RESULTS

Tables III and IV show by decade the age of the patient during the period of observation and the duration of the diabetes. Table V shows that as the total number of units of insulin increased the proportion of crystalline to protamine zinc insulin increased. Table VI shows the degree of control on separate injections, syringe mixtures and bottle mixtures.

These patients all used successively crystalline insulin and protamine zinc insulin (1) injected separately, (2) mixed thoroughly in a syringe immediately before injection and (3) premixed in a bottle. There-

fore, it was possible to make a comparison for better or worse of the control obtained on one arrangement or the other. In grading the control of this group of patients while under one of the preceding methods of insulin administration as compared with

TABLE III

Age in Years at Time of Study									
0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
13	46	37	32	21	44	26	7	2	228 patients

TABLE IV

Type of Diabetes	Duration of Diabetes							
	Duration in Years							
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	
Adult.....	48	62	20	17	6	2	1	
Juvenile.....	38	11	11	8	4	0	0	

TABLE V

Type of Diabetes	Proportion of Mixture	Total Dose of Insulin per Day Units							
		10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Adult	1:1	0	14	18	7	1	3	0	1
	3:2	0	13	13	17	8	5	2	1
	2:1	0	6	17	17	4	7	1	0
Juvenile	1:1	1	1	0	1	2	0	1	0
	3:2	1	1	2	4	4	3	3	2
	2:1	0	2	9	10	5	9	9	1
	3:1	0	0	0	0	1	0	0	0

another, it was evident that the highest percentage of patients were classified as under excellent control while using the bottle mixture.

Patients who use both crystalline insulin and protamine zinc insulin before breakfast are all anxious to use a mixture because of the simplicity and comfort of a single injection rather than two separate penetrations. Although this feature may be of interest to the clinician, if it is the only advantage of a mixture it is relatively inconsequential.

The most satisfactory insulin arrangement will be that which will give the most ideal control of the blood sugar throughout the twenty-four-hour period with the least number of injections and with the least deviation from the usual number of meals and their

TABLE VI

Type of Diabetes	Control with Separate Injections and with Mixtures			
	Comparison of Results	Separate Injection, Per Cent	Syringe Mixture, Per Cent	Bottle Mixture, Per Cent
Adult	Excellent	33	34.9	50
	Good	51	44.9	36.1
	Poor	16	20.2	13.9
Juvenile	Excellent	15.8	15.5	36
	Good	55.6	49.3	36
	Poor	28.6	35.2	28

respective food values. It is our impression at present that this is more satisfactorily accomplished by a mixture than it is by separate injections. Although it is true that the greatest percentage (78 per cent) of patients selected for the administration of mixtures seems, at present, to have the most satisfactory control on the 2:1 or the 3:2 proportion, it is possible to adjust the pharmacological action of the mixture to the individual patient by changing the proportions.

Further study of mixtures is indicated by the success of those who have employed them and have reported to date. More extensive data are necessary for full evaluation. It is expected that mixtures will be studied more widely in the diabetic clinics of the country in the next year or so. The decision as to whether mixtures will remain as a procedure in the care of diabetes in the future, or whether from these studies will

come data which will be the basis of a new formula for a slow-acting, long-acting insulin to replace the present standard protamine zinc insulin, will remain with the Toronto Insulin Committee. It would seem that such future decisions will be aided by studies of this kind.

SUMMARY

1. The data obtained by office observation of 72 juvenile and 156 adult diabetics while on syringe or bottle mixtures of crystalline insulin and standard protamine zinc insulin have been presented.

2. In general, mixtures either extemporaneous in the syringe or premixed in a bottle have proven to be a satisfactory method of administration for those patients requiring both quick-acting and long-acting insulins.

3. The data seem to suggest a preference for bottle mixtures.

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Myasthenia Gravis and Spontaneous Curarism*

Lipidystrophy as Possible Cause

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IN spite of extensive study, insight into the etiology of myasthenia gravis is still lacking. As the name implies, the disease manifests itself in a state of profound weakness of the muscles, those of the eyes, face and throat, as a rule, being involved first. The affected muscles show large collections of lymphocytes among the fibers which neither deteriorate nor atrophy nor do they show the reaction of degeneration. When these muscles are stimulated by faradic current, repeated at intervals of seconds, the muscular contractions become weaker with each stimulation and soon disappear. The thymus gland is frequently found enlarged, its activity being related in some manner to the lymphocytic infiltration of the muscle.

Preliminary data show that some marked fault in lipid metabolism may be an initiating factor through the release into the tissues of a lipid-cleavage product with curare effect. Some of these products also exert positive chemotaxis on the lymphocytes, the collections of lymphocytes among the muscle fibers being correlated with the observation that the lymphocyte possesses a special lipolytic enzyme to break down alien lipid material. The typical curare action consists essentially of an interruption of nerve impulses to muscle. This interruption takes place at the termination of the nerve fibers at the muscle cells. This effect probably consists in a neutralization of the

acetylcholine reaction which constitutes the fundamental neuromuscular stimulation mechanism.

Myasthenia is accompanied by a high degree of creatinuria and a reduction in creatinine. Administered creatine is practically all excreted as such apparently through failure to store it properly. Glycine is the precursor of creatine, the site of production of the latter being in the muscle. Muscle hypoglycinoses in myasthenia no doubt results from too rapid conversion of glycine to creatine, for the feeding of glycine stimulates creatine excretion. A correlation exists between glycine breakdown and creatine excretion. Its appearance in the urine after glycine tolerance tests is of great diagnostic value in myasthenia, muscle atrophies of the Charcot-Marie type, progressive muscular atrophy, congenital and other myotonias and also in the exanthemata, prolonged fevers, etc. Glycine is normally involved in the intermediary metabolism of carbohydrates and it increases the oxygen capacity. It also serves, like sulfhydryl, in cellular respiration, in the biological phenomena of oxidation-reduction, and in detoxifying processes of the body. In these toxic states there is a considerable drain upon the glycine and sulfur stores for detoxication purposes which leads eventually to such deficiencies.

Although remissions occur in myasthenia,

* The opinions or assertions contained herein are the private ones of the author and do not necessarily reflect the views of the Veterans Administration.

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death eventually results from paralysis of the respiratory muscles. The disease is often relieved during pregnancy but returns after delivery, the improvement being associated with improvement in creatine metabolism and the increased body lipid level. Creatine is normally found in the blood plasma in pregnancy and in the young in whom both plasma creatine and phospholipid values are high. From birth to puberty creatine is excreted but thereafter creatinuria is abnormal. Creatine is found in brain tissue, gray matter being far richer than the white matter. It is considerably increased in the blood of catatonic patients showing marked rigidity, whereas low creatine values are found in deteriorating dementia praecox and involutional melancholia.¹ In many brain and nerve disorders, the tissues also show lymphocytic infiltration which is apparently the result of abnormal lipid metabolism and disturbances in creatine and glycine metabolism.

A recent concept of myasthenia is that the fundamental disorder is not primarily in the central nervous system but in the motor fibers of the peripheral nerves and the muscle end plates where acetylcholine is liberated and then destroyed by the enzyme cholinesterase. There is also some evidence that the enzyme choline-acetylase, which synthesizes acetylcholine under anaerobic conditions, is inactivated by some toxic agent to prevent acetylcholine synthesis, the muscle then becoming refractory to cholinergic stimulation. The myoneural junction interposed between nerve fiber and muscle is a region in which conductivity is difficult and readily modified, so that it may be the seat of summation, inhibition and fatigue. The depression of cholinesterase activity, therefore, would be an important accompaniment of therapeutic improvement in muscles which have become refractory to cholinergic stimulation.

Ordinarily, the transmission of nerve im-

pulses at the myoneural junction depends on the liberation of acetylcholine, $C_7H_{17}NO_3$, an important lipid component. In myasthenia there is either an insufficiency through failure in acetylcholine synthesis or else it is rapidly destroyed by cholinesterase at the myoneural junction. Normally, stimulation at the motor nerve endings in voluntary muscle causes the liberation of acetylcholine which induces muscular contraction. As each nerve impulse transmitted along a preganglionic fiber causes but one impulse to be discharged along the postganglionic fiber, it is assumed that a fresh quantity of acetylcholine is liberated by each preganglionic impulse and is then destroyed by the action of cholinesterase. It is generally accepted that acetylcholine is liberated from the nerve terminals rather than from cells in relation to them, but whether or not it is liberated from a preformed store or is synthesized by the nerve impulse is not known. The brevity of time available for such a process speaks against the latter mechanism. Acetylcholine production may not keep pace with the concentration of cholinesterase although in myasthenia this enzyme is not found to be above normal concentration. Acetylcholine has great physiological importance as a parasympathetic stimulant but the ease with which it is hydrolyzed to inert choline and acetic acid prevents its extensive therapeutic use.¹

It is not within the scope of this paper to discuss as complex a subject as the phenomenon of nerve-impulse transmission but rather to point out some morbid metabolic disturbances of the body lipids that may have an important bearing on the genesis of myasthenia gravis.

LIPIDYSTROPHIES

The important lipids such as the phospholipids, lipoproteins, glycolipids, lecithin, cephalin, sphingomyelin, the cerebrosides, etc., are found extensively throughout the

animal and vegetable kingdoms. They are present in the human body in much larger amount in the brain and nerve tissue than elsewhere. The lipid values decrease during fasting, acidotic states, anoxia, etc., and are adversely affected by certain enzymes and hormones; insulin and thyroxin decreasing the lipid values. In fatigued muscle the lipids become greatly reduced, with an increase in ammonia probably arising from lipid breakdown.

In general, the lipids act as agents for the transport of oxygen within the cells and serve also as supplementary or intermediary agents (co-enzymes) to activate various enzymes. They also exert a protective effect against bacterial and viral toxins. The antioxidant lecithin plays an important rôle in cellular activity and the transfer and metabolism of fatty and carbohydrate material in the body. It is concerned in the metabolism of vitamin A, $C_{20}H_{30}O$, an unsaturated aliphatic alcohol which is synthesized from carotene and a chromolipid hydrocarbon, $C_{40}H_{56}$. Vitamin A increases the serum lipid level, acting as an oxidation-reduction catalyst to influence the utilization of lipid material. Avitaminosis-A, by causing hypolipidosis and abnormality of the lipids, results in a condition resembling subacute combined degeneration of the spinal cord. Lack of this vitamin also causes inadequate production and regeneration of the chromolipid visual purple in the retinal rod cells and thus causes night blindness. With this condition there is noted vasoconstriction of the retinal arteries and an accompanying photophobia through some little understood photochemical effect that disturbs the acid-base balance.³ Illumination of the eyes causes bleaching of visual purple and an alteration in the pH from alkaline to acid; the pH of the retinal tissue falling further as the light intensity is increased. Certain dietary lipid-deficiency symptoms resemble those induced by vitamin A and E deficiency

and can be alleviated by the administration of such fatty acids of animal lipid origin as linoleic, stearic and arachidonic acids. The latter, $C_{20}H_{32}O_2$, conceivably is synthesized to vitamin A. Favorable effects have been reported through use of vitamin E in some of the myopathies with improvement in creatine metabolism.

The lipids are more or less unstable and in certain morbid processes readily undergo derangement and breakdown with the release of numerous toxic degradation products. Some of these lipid cleavage products are highly lytic while others exert curare-like effects. A third group of such products exert selective tetanic effects upon the synapses to lower synaptic resistance and convert inhibition into active contraction. The latter morbid effects are observed in both tetanus and rabies infections where the toxigenic enzymes of these pathogens under anaerobiosis selectively seek from the nerve tissue such lipid components as lecithin, acetylcholine, choline, neurine, etc., to break down to cleavage products of highly tetanic nature. The progressive enzymic decomposition of these nerve bases along appropriate nerve tracts would explain the manner in which these toxins, reach the brain to produce the symptoms of the disease.² The recognized therapy of these two diseases if instituted early inhibits the production of tetanus and rabies toxins, an effect like that of extinguishing a fuse to prevent a disastrous explosion. The muscle rigors in both diseases cause excess production of organic acids, such as lactic acid, that further cell fluid absorption, spasmodic contraction and nerve irritation. Another factor in the muscle rigors is the increased output of acetylcholine at the myoneural junction and the inactivation of cholinesterase which normally serves to destroy acetylcholine but is itself inactivated by the changed pH of the tissues. Eventually, the hypothalamus and cerebral cortex become

affected, seriously interfering with the fronto-pontine tracts conveying impulses that normally serve to release muscular rigidity.²

When the lipids are acted upon and lose a fatty acid group, highly hemolytic substances such as lysolecithin, lysocephalin and lysosphingomyelin are formed. These lysolipins are capable of lysing cells through their great affinity for water and other fluids which on entering the cells cause swelling and rupture of the cell membranes. The more acid these fluids become the greater is the cell imbibition. The lysolipins combine readily with cholesterol, molecule for molecule, such combinations then becoming antitoxic agents with no further lytic power. Cholesterol, in addition to its protective action against cell lysis, is also concerned with the body's reaction to infectious diseases and with the processes of immunity.

SPONTANEOUS CURARISM

Several investigators have suggested the possible presence in the blood or tissues of myasthenic patients of some toxic substance that blocks synaptic transmission, raising the threshold of skeletal muscle to the effect of acetylcholine.⁴⁻⁷ However, such a toxic agent has eluded detection.

Recent study tends to show that a myoneural toxin is a major factor in the etiology of myasthenia gravis and that it is a cleavage product resulting from some abnormality in the cell lipids. The quaternary ammonium compounds such as acetylcholine, choline and other components of lipids like sphingosine and stearamide are the precursors of several myoneurotoxins. Acetylcholine induces muscular contraction and some of its derivatives often cause severe muscle hypertonicity. Other toxins similarly derived exert curare-like effects. The latter effect no doubt is dependent upon the pentavalent nitrogen, or rather the stereo-chemic orientation of the valences, while the hypertonic effects depend upon different

orientations. These imply phenomena that are rather difficult to explain fully upon biochemical grounds. The choline-derived myoneural toxins with curare-like effect, such as botulinine, mytilotoxin, muscarine and coniine, and the similarly acting tetramethyl-ammonium bases such as guanidine and methyl-guanidine interrupt the nervous impulses at the termination of the nerve fibers at the muscular cells. Sphingosine, $C_{18}H_{37}NO_2$, an important amino alcohol, is a component of sphingomyelin, the latter also being composed of choline and the fatty stearic acid radical. Its stearamide, $C_{18}H_{37}NO$, and the anhydride, stearonitrile, $C_{18}H_{35}N$, bear close structural relationships to curarine ($C_{18}H_{35}N$) if not having similar effects. Under what conditions nitriles may be formed from amines and amides is yet to be discovered.

What may be of considerable significance in myasthenia are the large collections of lymphocytes among the muscle fibers. These are usually indicative of the presence of toxic or alien lipid material, being correlated with the presence in the lymphocyte of a special lipolytic enzyme capable of breaking down morbid lipid products. These lipid products are positive chemotactic agents that cause attraction of the lymphocytes. Local collections of lymphocytes usually occur in and about lesions caused by bacteria that contain lipid material, notably the tubercle and lepra bacilli. These pathogenic agents are well protected by their lipid waxy capsules, surviving even in 15 per cent concentrations of sulfuric acid that will kill all other bacteria. The lipolytic enzymes of the lymphocytes are capable of completely lysing the waxy material if not inactivated by the accumulated cleavage products of their enzymic activities.

CURARE AGENTS

Drugs with curare action counteract the effects of spasm-producing agents by increasing the refractory period. Magnesium

compounds, quinine, nicotine, lobeline, gelsemium, coniine, muscarine, guanidine, methylguanidine and erythroidine exert depressant action on the peripheral ends of the motor nerves to control muscle spasm. Atropine prevents spasm apparently by acting upon the effector cells and antagonizing acetylcholine but does not prevent its liberation at the nerve terminals. In botulism and mussel and conium poisoning the absorbed preformed choline-derived alkaloids exert curare-like effects upon the nerve endings in the parasympathetic system. These toxins produce typical myasthenic symptoms and cause degenerative changes in the motor cells of the medulla and spinal cord not unlike those observed in poliomyelitis, acute encephalitis and other conditions which arise from certain viral infections. The toxins formed by the neurotropic viruses probably result from the interactions of their enzymes with specific nerve and brain lipid components susceptible to their influences.

Curarine, the active principle of curare, exerts a specific effect upon the motor endplates by raising the threshold of skeletal muscles to the effects of acetylcholine. Death is caused through paralysis of the respiratory muscles by the blocking of the passage of nerve impulses across the myoneural junction. Curare also lowers the output of epinephrine from the suprarenal gland and has been used in the treatment of certain hypertensive states that result from hyperadrenia. It has considerable therapeutic value in the early muscle spasms of poliomyelitis, athetosis, tetanus, rabies, maniacal outbursts, myoclonias and hypertonic states, convulsions and arachnidism, as well as counteracting the effects of spasm-producing drugs such as strychnine and metrazol. Strychnine has a marked affinity for cholinesterase, destroying its activity and permitting acetylcholine to exert its full stimulatory effect at the motor nerve endings.

In curare poisoning the muscles least affected are those which contain the largest amount of utilizable oxygen, these surviving the longest after death of the animal. Any myopathy that causes lowered oxygen supply prevents fatigued muscle from obtaining oxygen necessary to its recuperative powers; such tissue is then rendered more likely to be susceptible to the depressing effect of curare. Myasthenic cases are extremely sensitive to curare (this hypersensitivity being utilized in a two-minute diagnostic test for myasthenia gravis) since one-fifteenth to one-fifth of the average dose (Intocostrin*) given intravenously produces a profound exaggeration of symptoms and may add new symptoms not previously exhibited in a myasthenic patient.

The effects of curare are counteracted by the quaternary ammonium compound physostigmine which stimulates the myoneural junction. Physostigmine and like compounds might provide a biochemical means of counteracting the myoneural toxins of botulism, mussel poisoning and certain mushroom poisonings that exert curare effects. Neostigmine causes dramatic improvement in myasthenia gravis by augmenting the effect of acetylcholine, stimulating the myoneural junction and temporarily depressing cholinesterase activity. What effect it might exert on the lipolytic activity of the lymphocytes has yet to be determined. The effect of one injection persists about eight hours and may be prolonged if given in a vehicle to lessen the rate of systemic absorption. The action of physostigmine preparations is enhanced by glycine, ephedrine, antuitrine benzedrine, acetylcholine and potassium salts, the latter ions serving to stimulate the ganglion cells and increase acetylcholine production. Neostigmine and curare are of therapeutic value in relieving the early muscle spasms of poliomyelitis. Although their physiological effects are

* Squibb purified extract of curare.

opposed to one another, they relieve muscular spasticities probably by acting upon the synapses in the spinal cord to decrease fatigue, increase muscle tonus and relieve pain.

CONCLUSIONS

1. The primary disturbance in myasthenia gravis may be a lipidystrophy resulting from an abnormality in lipid metabolism. Through a fault in the cellular metabolism of such lipid components as choline, acetylcholine and sphingosine a myoneural cleavage product with curare-like action is released in the tissues. Transmission of the motor impulse at the myoneural junction is then blocked, raising the threshold of skeletal muscle to the effect of acetylcholine.

2. There is a migration, infiltration and collection of lymphocytes in the muscle fibers in myasthenia gravis. The lymphocyte possesses a lipolytic enzyme capable of breaking down alien lipid derivatives.

3. Glycine is the precursor of creatine, which is produced in muscle where it is chiefly stored for proper muscle tonus.

Creatinuria is an index of abnormal glycine breakdown in myasthenia and other myopathies.

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The Jejunal Syndrome*

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THE wider use of partial resection of the stomach for the treatment of peptic ulcer directs our attention to a disorder which was termed "dumping" syndrome by Eusterman and Balfour.¹ It has been recently discussed by Snell,² Glaesner,³ Schwartz, Reingold and Necheles,⁴ Jordan,⁵ Miller,⁶ Church and Hinton,⁷ Berkman and Heck.⁸ The patients become tired and sleepy after meals; they are nauseated, have a feeling of pressure in the stomach area, complain of heat and perspire abundantly. Some cases show tachycardia, fall in blood pressure, and even fainting and syncope occur. This syndrome has been explained as caused by distention of the jejunum, "dumped" with food from the anastomosed stomach; therefore the term "dumping" syndrome.

I encountered the syndrome as far back as in the twenties when studying the pathology and symptomatology of disorders of the small intestine. I followed up cases of acute enterocolitis. After subsidence of the diarrhea the feces became normal as regards their macroscopic appearance, the physical and x-ray examination of the colon did not reveal any pathology. But certain complaints and symptoms persisted pointing to the small intestines as the site of the disorder. Furthermore, I observed the same symptoms in numerous other patients without antecedent enterocolitis. I supposed this distress to be a catarrh of the small intestines.^{9,10,11,12} I called it enteritis in distinction to catarrh of the large intestines, colitis. There is no anatomic confirmation of my conception, but animal experiments

of Mahler, Nonnenbruch and Weiser¹³ point to a frequent occurrence of enteritis. These authors gave spices such as pepper and paprika to dogs by mouth and examined the mucous membrane of the jejunum the day after. They saw a reddened, swollen mucosa with numerous ecchymoses and the villi were paralysed. As a matter of fact, the syndrome which I described as enteritis is rather frequent and, I dare say, every physician must have seen these cases although they may not be recognized but diagnosed as indigestion or nervous stomach or spasticity of the colon or some other disorder.

From the complaints of the patients, I distinguished the following groups: (1) Enteritis imitating gastritis. The patient complains of poor appetite, epigastralgia and nausea. He is sensitive to heavy food and may vomit at times after heavy meals. (2) Enteritis imitating peptic ulcer. The patient complains of colicky pains occurring a short while after eating, radiating to the left upper abdomen. These pains last only a few minutes but may recur, whereas ulcer pains last for hours. Unlike ulcer pains they are not relieved by food and alkaline drugs. (3) The syndrome described above as "dumping" syndrome. Patients in this category are rare compared with the number in the other groups of enteritis.

Physical examination in enteritis reveals tenderness of the left side of the abdominal wall at the level of the umbilicus, which I have called "jejunal pressure point." The best way of checking it is to have the patient lift himself from a supine to a semi-sitting position without support of his arms, where-

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upon the abdominal muscles stay contracted. Different points of the rectus muscle are pressed with the thumb and the patient is asked which one is the most sensitive. In cases of jejunitis the point to the left of the umbilicus is most sensitive. In cases of ileitis the pressure point is to the right of the umbilicus. There is a pressure point on the back to the left of the twelfth vertebra in some cases of jejunitis. The most important test for the diagnosis of enteritis is the microscopic examination of the feces. The stool may be formed. In cases associated with constipation it is hard and dry; the color may be normal, dark brown, except for severe cases who have light yellow feces. The microscopic examination reveals numerous soaps as crystals in the form of blunt needles, sometimes mixed with slender needles of fatty acids. In the healthy state, as is well known, there are hardly any soap crystals in the feces and only a few soap globules. In severe cases of enteritis with yellow feces the microscopic picture resembles that in icterus; the field is covered with soap crystals. Roentgen examination reveals accelerated passage through the small intestines in many cases of enteritis; two hours after intake barium has already reached the colon.

The increase of soaps in the stool points to impaired absorption in the small intestines. There may not be enough time for complete absorption because of accelerated transportation or there may be a functional impairment of absorption, or both. Sprue, another disease of the small intestine, is known to be accompanied by soapy feces. From this point of view, enteritis and sprue may be the same condition, differing only in the degree and extent of the impairment and probably in the etiology, the latter being associated with vitamin deficiency. Severe enteritis may turn into sprue either by failure of absorption of vitamins or because of insufficient supply of vitamins with the food,

or both. Enteritis itself is, according to my experience, in no way connected with vitamin deficiency and cannot be cured by vitamin medication.

I described briefly the clinical pathology of enteritis because the same symptoms may be encountered in cases of resected stomach. Among the disorders observed in those patients is a group with epigastralgia, nausea and poor appetite, simulating gastritis. Berkman and Heck⁸ describe instances of such complaints. There is another group complaining of pains radiating to the left abdomen suggesting jejunal ulcer, and finally there are cases of the "dumping" syndrome. The explanation of this last complaint as being caused by distention of the jejunum has been questioned by Berkman and Heck. While all instances of resected stomach observed by these authors revealed "dumping" of the jejunum, only 5.6 per cent of their 500 cases suffered from this symptom. Moreover, I have seen patients without resection of the stomach and without "dumping" presenting the same syndrome. The emptying of the stomach and filling of the jejunum was completely normal in these patients. The following case is an example of "dumping" syndrome without dumping.

CASE REPORT

A male, aged forty-three, had an attack of diarrhea two years ago, with six to ten bowel movements a day. After a week of bland diet, the diarrhea ceased and he has had normal bowel movements since. There was some indigestion after meals during the next weeks which became gradually worse and within two months the "dumping" syndrome developed: Tired feeling, hot flushes and perspiration after meals. At times the patient became dizzy and had to lie down. We observed him after meals and saw his face covered with beads of sweat, his shirt soaking wet from perspiration. The examination revealed an underweight man of normal skin, normal complexion, normal body build. The physical examination of the mouth and

chest organs did not show pathology. There was a tender pressure point of the left rectus abdominis at the navel level. The gastric analysis was normal. The feces were formed, light yellow. The microscopic examination revealed abundant small blunt soap crystals and some digested muscle fibers. With roentgen rays normal outlines of the stomach and intestines, normal motility and emptying of the stomach were seen. The patient took barium and right after the stomach examination a veal chop with potatoes. Two hours after taking barium one third of the barium was still in the stomach, traces were in the jejunum, and the bulk was in the ileum, cecum and ascending colon.

The attack of diarrhea at the onset of the disease very likely was acute enterocolitis. The colitis cleared up as proved by the subsidence of the diarrhea, but the enteritis continued and became worse, as indicated by the development of the "dumping" syndrome. This and other cases prove that the syndrome can occur without "dumping." But "dumping" may be an important factor after gastric resection, not so much mechanically by distention of the jejunum, but in producing enteritis. Unprepared and indigested food may be the cause of enteritis not only in cases of resected stomach, but in patients with jejunostomy as well, in which, according to observations of Alvarez¹⁴ and other authors, the syndrome can be induced by jejunal feeding. Undigested food poured directly into the jejunum may elicit a reaction even from the normal mucous membrane of the gut. Another factor producing enteritis may be the kind of food given to resected patients before the distress started. Too hot or too cold food or drinks, spices, roughage may cause damage to the mucous membrane of the jejunum, and, if repeated, may produce jejunitis. This may explain why only some of the resected patients suffer this kind of distress. Besides there may have been enteritis before the resection of the stomach in some cases, and the "dumping" may have aggravated the disease.

All my cases of "dumping" syndrome, resected and unresected alike, revealed the signs and symptoms described above: The jejunal pressure point, increased soaps in the feces and accelerated passage through the small intestines, whereas resected patients without complaints did not show those symptoms.

According to the aforementioned observations "dumping" may not be the direct cause of the syndrome, the distress rather may be due to jejunitis, produced of course by the failure of digestion and preparation of the food in the stomach. Therefore, I would propose abandoning the term "dumping" and call it "jejunal syndrome." For the symptoms of tachycardia, drop of blood pressure, dizziness, fainting, I used the term "jejunal shock."^{11,12}

As pointed out above, the jejunal syndrome is rare, whereas enteritis is a rather common disease. In the majority of cases the distress is not severe, and there are many instances with no complaints at all. Slight gastritis-like symptoms are the complaints most frequently encountered. The disease is of more importance because of complications and sequelae. Flatulence is often present. It may be caused by the accelerated passage through the small intestines, so that more undigested carbohydrates are carried into the colon and fermented there by bacteria producing gases. The disease may descend into the cecum causing tenderness of this area and later to the lower colon, whereupon diarrhea sets in. Bacteria may gain entrance into the portal circulation from the inflamed mucosa of the small intestines and may be carried into the liver and bile, infecting the gall bladder and bile passages, and cholelithiasis may result.

SUMMARY

1. The "dumping" syndrome observed in patients after resection of the stomach is a syndrome due to severe enteritis or jejunitis

and may be seen in cases without resection of the stomach.

2. Enteritis is a frequent disorder. The "dumping" syndrome is rare whereas complaints simulating gastritis or peptic ulcer are more often encountered.

3. The signs of enteritis are briefly described.

4. The use of the term "jejunal syndrome" instead of "dumping" syndrome is suggested.

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The Use of an Injector Meter for Maintenance of a Prescribed Oxygen Concentration and Elimination of Carbon Dioxide in Closed Head Tents*

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THE open box for administration of oxygen, originally described by Burgess,¹ was subsequently modified by him and his collaborators by closing the top of the tent with a rubber cover in order to administer high concentrations of oxygen.² The carbon dioxide was at first removed by soda lime contained within the apparatus, the heat and moisture by an ice rack. Later, Saklad and Burgess³ used an injector from the oxygen cylinder to circulate the oxygen enriched atmosphere through a soda lime container outside the tent. Since employment of soda lime requires frequent testing of carbon dioxide concentrations within the tent, it seemed more convenient to use an injector attached to the regulator to furnish sufficient oxygen and outside air to wash out the carbon dioxide given off by the patient.

In large tents with motor-blower circulation, a flow of 15 liters per minute for twenty minutes, with a maintenance flow of 10 liters per minute, is generally adequate to maintain an oxygen concentration of 50 per cent and reduce the carbon dioxide concentration below 1 per cent. This is made possible by the fact that a considerable diffusion takes place under the canopy at its

contact with the bed clothes and through the mattress.

In the closed head tent there is virtually no entrance of gas into the tent other than that being delivered from the oxygen regulator. Thus, with a patient who is eliminat-

TABLE I

Percentage Setting	Air Intake per Liter of Oxygen Flow
40	3.14
45	2.28
50	1.72
60	1.02
70	0.61
80	0.34
90	0.14

ing 200 cc. of carbon dioxide per minute, a flow of 20 liters of gas per minute would be required to dilute the exhaled carbon dioxide to a percentage level of approximately 1 per cent. If pure oxygen were run into the tent at this rate of flow, the percentage in the tent would soon reach 95 per cent or more. With the use of the injector, however, large volumes of gas may be admitted into the tent without the need for large oxygen flows and with percentages of oxygen in the inhaled atmosphere corresponding to those set by the injector, as produced in the Meter mask assembly.⁴

A Meter, i.e., injector, will mix a definite

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volume of air with oxygen depending on the percentage setting. These volumes are shown in Table I. To obtain a total gas flow of 20 liters per minute with a 40 per cent mixture, a flow of only $\frac{20}{1 + 3.14}$, approxi-

weight and age category (first three lines in Table II) and read flow requirements on this line under the appropriate percentage desired. For example, an eight-year old child weighing fifty-seven pounds and measuring 4 feet 2 inches in height would be nearest

TABLE II
FLOWS OF OXYGEN REQUIRED FOR CONCENTRATIONS BETWEEN 40 AND 100 PER CENT IN CHILDREN AND ADULTS, CALCULATED ON THE HEIGHT-WEIGHT RATIO*

Age	Height	Weight (lb.)	Estimated CO ₂ Output	Oxygen Flow in Liters Per Minute							
				40%	45%	50%	60%	70%	80%	90%	100%
5.....	3'7"	41	156	4.0	5.0	5.5	7.5	9.5	11.5	12.5	15.5
10.....	4'5"	68	206	5.0	6.5	7.5	10.0	12.5	15.5	18.0	20.5
15.....	5'5"	123	281	7.0	8.5	10.5	14.0	17.5	21.0	24.5	28.0
Small adult.....	5'2"	130	231	5.5	7.0	8.5	11.5	14.5	17.0	20.0	23.0
Medium adult.....	5'7"	148	259	6.5	8.0	9.5	13.0	16.0	19.5	23.0	26.0
Large adult.....	6'2"	184	308	7.5	9.5	11.5	15.5	19.5	23.0	27.0	31.0

* The table was prepared as follows: The average height, weight and age relationships were obtained from tables prepared by Dr. Bird T. Baldwin and Dr. Thomas Wood. These tables are published by the American Child Health Association. Additional data regarding height and weight was obtained from "Personal Health Standard and Scale" by Dr. Thomas Wood and published by the Bureau of Publications, Teachers College, Columbia University. Values for males were chosen since they were higher for each of the categories shown.

Surface areas and oxygen consumption values (not shown in Table) were calculated from Dubois body surface area and normal standard charts.

The probable carbon dioxide output was calculated from the oxygen consumption values. An RQ of 0.9 and an increase of 25 per cent in the carbon dioxide output above basal conditions was assumed.

mately 4.8 liters per minute of oxygen is required. Under these conditions the oxygen concentration in the closed head tent would be very close to 40 per cent.

We have listed the height, weight and age of various groups of patients in Table II. The oxygen flow rate requirements for various oxygen percentages for these groups are likewise listed. With these suggested flows the carbon dioxide levels in the tent will be approximately 1 per cent. If lower or higher carbon dioxide levels are desired, increase or decrease the suggested oxygen flow rates by the following formula:

$$\frac{\text{Oxygen flow rate} \times 1}{\text{CO}_2 \text{ percentage desired}}$$

To use this chart determine the age, height and weight of the patient. If fifteen years or under, choose nearest height;

the ten-year old category. If 50 per cent oxygen were prescribed the flow required (use second line and 50 per cent column) would be 7.5 liters per minute. For patients over fifteen years of age use last three lines in Table II. The suggested oxygen flows shown in the body of Table II will provide the oxygen percentages shown at the top. The carbon dioxide level in the hood will be approximately 1 per cent.

The apparatus is illustrated in the accompanying photographs. (Figs. 1 and 2.) The injector or Meter is attached to the oxygen regulator and connected to the head tent by $\frac{3}{8}$ inch bore tubing. The ice rack contains sufficient ice to provide adequate cooling for a three-hour period. Insulated ice racks of larger capacity can be procured. The transparent canopy adds to the comfort of the patient and permits ready observation.

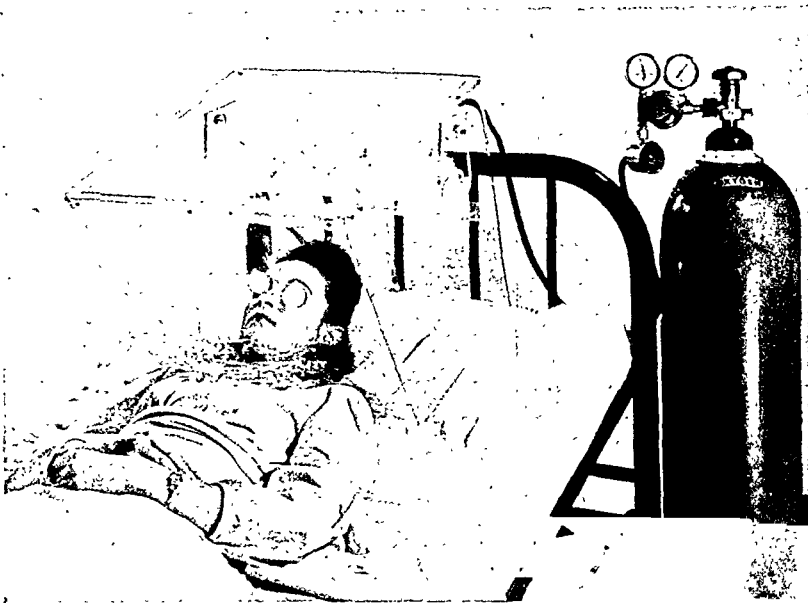


FIG. 1. Closed head tent with plastic ice rack and injector (attached to the regulator) for delivery of the prescribed oxygen concentration.

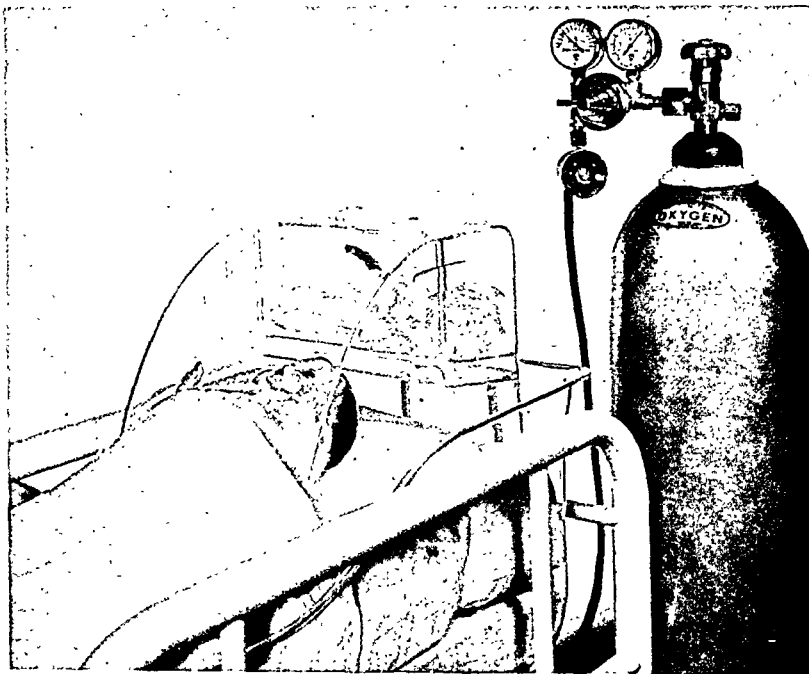


FIG. 2. Infant model of the closed head tent with ice rack and oxygen concentration meter.

The plastic now employed is torn only with great difficulty. Oxygen percentages in the tent reach the level of the percentage settings

The prescribed oxygen concentration is maintained in the tent by setting the injector (Meter) between 40 and 100 per cent.

PATIENT	HEIGHT INCHES	WEIGHT POUNDS	CO ₂ OUTPUT CC. PER MINUTE
LARGE ADULT	74	184	
MEDIUM ADULT	67	148	
SMALL ADULT	62	130	
CHILD OF 10 YEARS	53	68	
CHILD OF 5 YEARS	43	41	

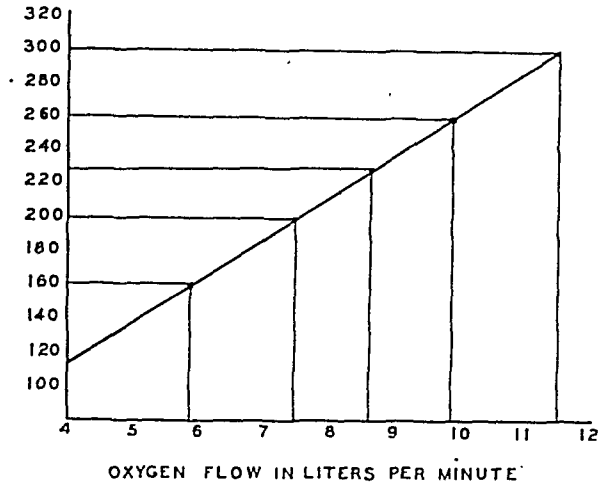


FIG. 3. Oxygen flow requirement to provide 50% oxygen in different sized adults and children.

of the Meter within fifteen minutes after onset of flow of gas.

The oxygen flow requirement to provide 50 per cent oxygen in different sized adults and children is shown in Figure 3.

SUMMARY

A head tent is described in which an injector is used for the purpose of adding a combined oxygen and air atmosphere adequate to wash out carbon dioxide exhaled by the patient.

The apparatus is comfortable, effective and relatively inexpensive.

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The Effect of Propylene Glycol on the Antibiotic Activity of Human Serum^{*}

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STUDIES with penicillin aerosol, obtained by means of a combined steam generator and aerosolizer,^{1,2} disclosed that penicillin, dissolved in propylene glycol 19 parts and glycerine 1 part, produces a stable aerosol. Unusually high "penicillin" blood levels of long duration were obtained by keeping the patient for one hour in a tent into which this penicillin-propylene glycol aerosol was blown, or by making him inhale by means of a tube and mask from a box into which the aerosol was blown and confined.³ (Table I.) The determination of antibiotic activity in these and all experiments recorded below were made according to the method described by Randall, Price and Welch,⁴ which makes use of a certain strain of *B. subtilis* as the organism for determining penicillin-like activity.

Because of these very high, long, sustained values, similar studies were made with propylene glycol and glycerol respectively. These revealed that propylene glycol, when inhaled as an aerosol, imparted antibiotic activity to the blood of patients whose sera were previously inactive. (Table I.) The antibiotic potency of the propylene glycol in vitro before aerosolization was 0.031 units, which is considerably less than the value of 0.5 units repeatedly obtained by inhalation of the aerosol. (Table I.)

Table I also shows that in the aerosols containing penicillin, the antibiotic properties of the blood were not entirely due to the

glycol. When the amount of propylene glycol was kept constant, the addition of penicillin invariably increased such antibiotic activity; that is, raised the levels of "penicillin" in the blood.

Propylene glycol was then given to pa-

TABLE I
"PENICILLIN" BLOOD LEVELS OBTAINED BY INHALATION
OF PENICILLIN-PROPYLENE GLYCOL AEROSOL

Method of Confining the Aerosol	Aerosol			"Penicillin" Blood Levels (Units/cc.)							
	Penicillin (Units)	Propylene Glycol (cc.)	Glycerol (cc.)	Time in Hours							
				½	1	2	3	4	5	6	
Tent*	100,000	19	1	.25	.25	.25	.25	.125	.125		
	200,000	19	1	.125	1.0	1.0	.5	.5	.5	.5	
Breathing Box†	50,000	19	1	1.0	1.0	1.0	1.0	1.0	1.0	.5	
	100,000	19	1	1.0	1.0	1.0	1.0	1.0	.5	.5	
	200,000	19	1	2.0	2.0	2.0	2.0	2.0	1.5	1.5	
	0	19	0	.5	.5	.5	.5	.25	.25	.25	
	0	19	0	.5	.5	.5	.5	.5	.5	.5	
	0	19	0	.5	.5	.5	.5	.5	.5	.25	
	0	0	1	0	.0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	

* Patient in the tent for 1 hour.

† Patient inhales from the box for about ½ hour.

tients orally, intravenously and intramuscularly. The antibiotic activity is recorded in Table II.

It is obvious that propylene glycol, when introduced into the body by pulmonary, intravenous or intramuscular routes, imparts

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to the blood some antibiotic activity lasting six hours.

In view of the fact that some normal human sera display natural antibiotic activity against *B. subtilis*,^{5,6} these sera were tested prior to treatment. Two of these sera

TABLE II

ANTIBIOTIC ACTIVITY OF HUMAN SERUM FOLLOWING ADMINISTRATION OF PROPYLENE GLYCOL ORALLY, INTRAMUSCULARLY AND INTRAVENOUSLY

Propylene Glycol			Antibiotic Activity of Serum (Units/cc.)								
Method of Adminis- tration	Amount (cc.)	Patient	Before Treat- ment	Time in hours							
				½	1	2	3	4	6	8	
Oral	10	G.	0	0	0	0	0	0			
	10	B.	0	0	0	0	0	0			
Intra- muscular	6	D.	0	5	5	.5	5	.5			
	5	M.C.	0 031	5	5	.5	..	5	25	0	
	5	D.S.	0	.5	5	.5		5	5	0	
Intra- venous	6	R.	0	1 0	1 0	1 0	1 0	1 0			
	5	F.	0	1 0	1 0	1 0	..	1 0	.5	0	
	5	P.C.	0 031	1 0	1 0	1 0	..	1 0	1 0	0	

(from patients M. C. and P. C.) showed initial antibiotic activity equivalent to 0.031 penicillin units per cc. prior to treatment. The actual antibiotic activity due to the presence of propylene glycol in these cases is, therefore, equal to that recorded in Table II minus 0.031 for each reading.

Inasmuch as undiluted propylene glycol repeatedly gave an antibacterial value of 0.031 units per cc., the effect of dilution upon its antibiotic activity was tested. Normal human serum, beef broth and water, respectively, were employed as diluents. The results are recorded in Table III.

It seems clear that dilution *per se* is not responsible for the antibiotic activity of the propylene glycol, but that the glycol and serum are jointly responsible. (Table III.)

As further evidence of the antibiotic activity of the propylene glycol-serum mix-

ture, ½ cc. of each of the dilutions with serum from 1 to 10 through 1 to 100,000,000 were incubated for twenty-four hours at 37°C. with 1½ cc. of a suspension of *B. subtilis* (1-100). No growth occurred in any dilution up to 1 to 10,000,000. Beyond this

TABLE III

ANTIBIOTIC ACTIVITY, IN VITRO, OF DILUTIONS OF PROPYLENE GLYCOL WITH SERUM, WATER AND BROTH

Dilution	Antibiotic Activity (Units/cc.)				
	Serum (4 Determinations)	Water (2 Determinations)	Beef Broth (1 Determination)	Un-diluted Propylene Glycol	Un-diluted Serum
1-10	0.25	0	0	.031	0
1-100	0.25	0	0		
1-1000	0.25	0	0		
1-10,000	0.25	0	0		
1-100,000	0.25	0	0		
1-1,000,000	0.25	0	0		
1-10,000,000	0.25				
1-100,000,000	0				

dilution there was growth. Identical results were obtained in three trials.

When a combined aerosol of penicillin and propylene glycol is administered (Table I), it is possible to estimate quantitatively the antibiotic effect of penicillin and propylene glycol respectively, by the use of penicillinase, which inactivates the penicillin. Thus, a patient was treated with an aerosol of 50,000 units of penicillin dissolved in 19 cc. of propylene glycol and 1 cc. of glycerol. Blood specimens were taken at ½ hour and 1 hour intervals. Half of each of these specimens was treated with penicillinase; the remainder was untreated. Estimation of antibiotic activity of these specimens revealed that the penicillinase-treated sera showed an antibiotic activity of 0.25 penicillin units per cc. (due to the glycol), whereas the untreated sera showed values of 0.5 penicillin units per cc. (expressing the com-

bined antibiotic activity of penicillin and propylene glycol).

Whether the same type of antibiotic effect of the propylene glycol serum mixture is exerted upon organisms other than the one employed in these experiments remains to be seen. Studies along these lines are now in progress.

These observations on the antibiotic activity of a propylene glycol aerosol coincide with the clinical experience of one of us (S. J. P.), who has been treating asthma and allergic rhinitis associated with infection in the respiratory tract with aerosols of penicillin-propylene glycol. For control purposes, some of the patients were treated with propylene glycol aerosol without penicillin and in a few instances favorable results were noted.

COMMENTS

The bactericidal properties of propylene glycol have been investigated by Robertson and his co-workers.^{7,8} They observed that whereas the liquid displayed rather low germicidal properties, except in concentrations of 80 per cent to 90 per cent, the aerosol was highly effective in dilutions of 1 Gm. of propylene glycol in two to four million cc. of air. The vapor of propylene glycol was even more effective, 1 Gm. in 10–20,000,000 cc. of air almost instantly sterilizing the atmosphere against a variety of organisms and the virus of influenza.⁸ The lethal action of the glycol in vapor form was explained by the high affinity of this glycol for water, with which it is miscible in all proportions. When the vapor contacted an organism, it quickly reached a concentration of 70 to 80 per cent within the cell, and thereby exerted its lethal action.

This does not account for the phenomenon observed when propylene glycol is mixed with normal human serum or plasma. Apparently, a combination of the glycol and some factor in the serum is effected, which results in antibiotic activity of a degree possessed by neither alone.

CONCLUSION

Propylene glycol in serum exerts marked bactericidal properties against a strain of *B. subtilis*. Such a degree of antibiotic activity (one part glycol to ten million parts serum) is displayed by neither glycol nor serum alone. This antibiotic activity is due possibly to a combination effected by the propylene glycol with some factor in the serum.

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Management of Acute Toxic Nephrosis

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ACUTE toxic nephrosis is the clinical syndrome produced by a particular type of acute renal injury. Clinically, it is manifested by decreased or absent urinary output, fluid retention, progressive azotemia, plethora, hypertension, cardiac dilatation and pulmonary edema. Variable degrees of albuminuria and abnormal urinary sediment are present, and the low specific gravity of the urine persists throughout and after the acute episode. The dominant pathological feature is acute, selective damage to renal tubular epithelium. The etiological agents are diverse,¹ as many as thirty-four according to Peters,² but the more clearly delineated ones are carbon tetrachloride poisoning, hemolytic transfusion reaction and crush syndrome. The mortality rate is high, yet when recovery occurs it is usually complete.^{1,3,4}

Confronted with the urgency of the acute disorder, the alternative of death or complete recovery of the patient, and the lack of specific therapy, the physician who seeks aid in the management of the critically ill patient is offered a bewildering variety of therapeutic suggestions. Some of these therapeutic suggestions are diametrically opposed in principle and the efficacy of all of them is disputed.

Since spontaneous recovery occurs, it would seem logical to accept this as a basic principle in the management of acute toxic nephrosis. Thus one may endeavor to determine which therapeutic measures may aid and which may harm spontaneous recovery. This basic concept also affords a standard for the critical evaluation of pro-

posed medical and surgical therapeutic procedures. The following case reports illustrate the feature of spontaneous recovery and indicate some of the problems of management.

CASE REPORTS

CASE I. *Acute Toxic Nephrosis Due to Carbon Tetrachloride.*⁴ This twenty-two year old soldier became acutely ill after two days of intermittent inhalation of carbon tetrachloride used in degreasing guns. Nine of fifteen men similarly exposed to this agent became acutely ill and eight of them recovered fully after forty-eight hours. This patient, however, progressed to renal insufficiency; in this connection, a past history of alcoholism is significant. About five hours after the last exposure to carbon tetrachloride, the patient had nausea, vomiting, dizziness, weakness, backache, pains radiating down the back of the legs, fever and tachycardia. He was hospitalized and received morphine sulphate, atropine sulphate, and repeated intravenous injections of 10 per cent glucose, physiological saline and calcium gluconate. On the third day of illness the symptoms were aggravated, abdominal pain and distention were additional complaints, and attention was directed for the first time to an oliguria. There was no improvement following repeated intravenous infusions. On the fourth day of illness, he was transferred to another hospital where he came under our observation.

Examination disclosed an apathetic, nauseated, drowsy patient with a temperature of 98.2°F., a pulse of 64 and respirations 24. The eyes were puffy, the sclerae subicteric and there was a urinous odor to the breath. Slight bleeding from the right nostril, moderate stomatitis, and an ulceration of the right tonsil

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were noted. The heart and lungs were normal. The blood pressure was 140/110. The abdomen was distended, the liver edge palpable one to two finger breadths below the costal border and tender. There was mild costovertebral tenderness. The kidneys were not palpated. The

The daily fluid intake of the first six days of illness ranged from 2,000 cc. to 3,720 cc. (average 2,600 cc.) and from the fourth to the eleventh day fluids were given chiefly intravenously. In addition to infusions of 5 per cent glucose alternately in saline and distilled water,

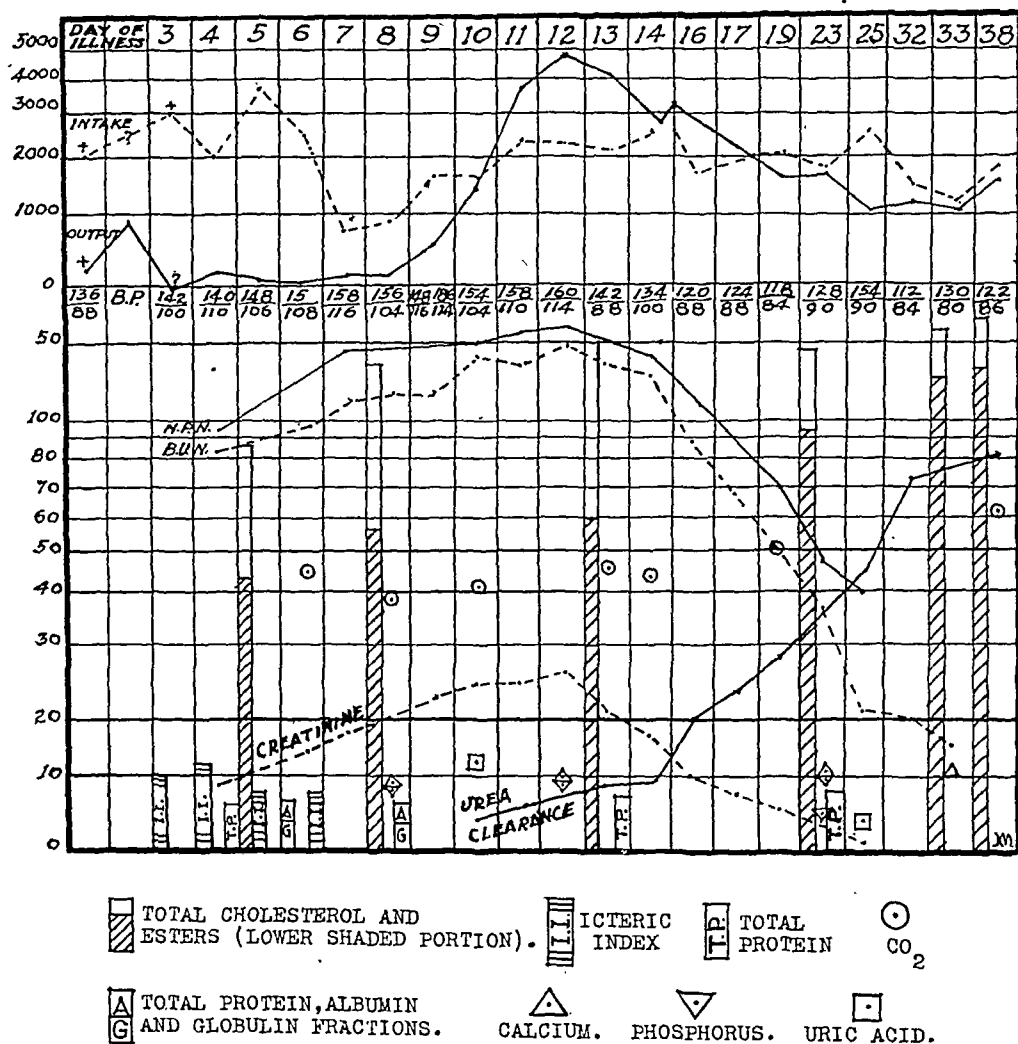


Fig. 1. Composite of intake, output, blood pressure and blood chemistry. Observations charted on semilogarithmic paper. Non-protein nitrogen, blood urea nitrogen, cholesterol and cholesterol esters, creatinine, calcium, phosphorus and uric acid recorded in mg. per cent; icteric index in conventional units; total protein in Gm. per cent; CO₂ in volumes per cent; urea clearance in per cent of average normal function.

history indicated anuria for the preceding twenty-four hours; severe oliguria was present and persisted. Laboratory studies corroborated the clinical impression of predominant renal insufficiency. (Fig. 1.) Details of fluid intake and output, blood pressure, blood chemistry and urea clearances are summarized in Figure 1.

the patient received 50 per cent glucose, 300 cc. of plasma and several injections daily of 10 cc. of 10 per cent calcium gluconate.

On the sixth day there was puffiness of the face and skin but no pitting edema. On the seventh day, the patient's condition appeared critical. Headache was a prominent complaint.

nausea and vomiting increased and he vomited a total of 180 cc. of frankly bloody material. A superficial scratch of the neck resulted in profuse bleeding that required compression. Epistaxis was another manifestation of this bleeding tendency that apparently responded to vitamin K since the bleeding tendency disappeared after forty-eight hours of administration of this vitamin. The pulmonic second sound was now accentuated and reduplicated; the blood pressure was 158/116. There was severe abdominal pain. The liver edge was enlarged to the umbilicus and markedly tender. Puffiness of the skin had increased, but there was no pitting edema and the lungs were clear. The blood non-protein nitrogen had risen to 146 mg. per cent, the urea nitrogen to 110 mg. per cent and the creatinine was 18 mg. per cent.

On this seventh day of illness it was decided to discontinue all intravenous fluids and allow the patient only a minimum of oral fluid. The patient felt better on the eighth day, although crackling râles were noted in the chest and pitting peripheral edema was present. There was cough with expectoration of thick, bloody, muco-purulent sputum. X-ray of the chest disclosed early pulmonary congestion, patches of bronchopneumonia and borderline cardiac enlargement. On the ninth day there was frank congestive failure, with numerous rales at both bases, probable ascites, markedly enlarged and tender liver, and pitting edema of the lower extremities and abdominal wall. A chest x-ray exhibited remarkable cardiac enlargement, increased pulmonary edema, bronchopneumonia and a small effusion at the right base. On this day there also occurred an alarming episode of forty-five minutes' duration in which there was confusion, severe headache, mild convulsions, progressive impairment of vision including transient blindness, and abrupt elevation of the blood pressure to 186 systolic and 124 diastolic.

The precarious state was still present on the tenth day. However, for the first time, the output approached the fluid intake. From the eleventh through the eighteenth day there was a striking diuresis of nearly twenty-six liters. With the onset of diuresis there was immediate and striking clinical improvement, the symptoms disappeared rapidly, the appetite returned promptly,

and clinical evidences of water retention disappeared within forty-eight hours. X-ray of the chest on the sixteenth day revealed the heart and lungs to be normal. A notable tissue weight loss was restored to normal within several weeks.

Improvement in the laboratory findings was not as spectacular. Actually, the maximum figures of nitrogen retention (non-protein nitrogen 173 mg. per cent, urea nitrogen 148 mg. per cent, and creatinine 26.4 mg. per cent) were obtained more than twenty-four hours after the onset of diuresis. The azotemia diminished relatively slowly and it was not until the twenty-fifth day of illness that the non-protein nitrogen and creatinine were normal, while the urea nitrogen did not become normal until the thirty-third day. On the thirty-third day the urea clearance was about 80 per cent of average normal, but the maximum specific gravity in the concentration test was only 1.020.

The clinical improvement that began with the diuresis continued rapidly to the complete restoration of health. After forty-five days of hospitalization, including a furlough, the patient was able to return to unlimited duty. All evidences of hepatic, renal and cardiac damage had disappeared, the blood pressure ranged from 112/84 to 130/80, the urea clearance test was 89 per cent of average normal function, and the maximum specific gravity of the urine concentration test was 1.024. (Fig. 1 and Table I.)

Comment. This case illustrates the typical acute renal insufficiency that occurs in about 23 per cent of the cases of carbon tetrachloride poisoning.⁵ The inhalation route of poisoning and alcoholism predispose to the development of this renal lesion.^{4,5} Although acute toxic manifestations, including gastrointestinal irritation and mild hepatic damage, were the initial presenting features, the acute toxic nephrosis predominated after forty-eight hours of illness. Oliguria and anuria were followed by fluid retention, hypertension, azotemia, edema and anasarca of renal, subsequently of cardiac and renal origins, rapid cardiac dilatation and decompensation, pulmonary

edema, hypertensive encephalopathy and bronchopneumonia.

Fluids were forced moderately for the first six days, averaging 2,600 cc. daily. From the fourth day, fluids were given chiefly by intravenous route and vomiting diminished. Oliguria, however, persisted and the patient's critical state and dubious prognosis evoked a conference on therapy on the seventh day. Numerous therapeutic procedures were discussed and serious consideration was given to (1) more vigorous administration of fluid, (2) hypertonic fluids, (3) diuretics, (4) lavage of renal pelvis, (5) decapsulation of kidneys and (6) sympathetic nerve block. Fortunately, none of these procedures was employed; the minority recommendation of fluid restriction was adopted. Fluid restriction at this stage, however, did not prevent cardiac dilatation, anasarca, pulmonary edema, and hypertensive encephalopathy that ensued after another forty-eight hours of oliguria; it did, undoubtedly, contribute to the eventual recovery.

The urinary output increased slightly on the ninth day, exceeded 1,000 cc. on the tenth day, and a striking, spontaneous diuresis of 26 liters occurred in the subsequent week. As soon as diuresis began, the clinical picture changed promptly, in a manner approaching a crisis. The abatement of the azotemia was not parallel. (Fig. 1.) On the sixteenth day the patient was virtually asymptomatic. He enjoyed a diet of 2,500 calories composed of 450 Gm. of carbohydrate, 50 Gm. of protein and 20 Gm. of fat. There was no evidence of water retention, no cardiac abnormality, and his blood pressure was 120/88, yet the elevation of non-protein nitrogen, urea nitrogen and creatinine was of the same magnitude as on the fourth day of illness.

There were other indications of damaged tubular epithelium aside from the slow excretion of nitrogenous products. In the oli-

guric, prediuretic phase, the urine specific gravity was constantly low, ranging from 1.007 to 1.009. The maximum urine specific gravity in the diuretic period increased to 1.014. The maximum specific gravity of the urine concentration test increased only slowly in the post-diuretic period: 1.018 on the twenty-fourth day, 1.020 on the thirty-third day, and 1.024 on the thirty-eighth day. The return of the ability to excrete water was not accompanied by an equivalent ability to excrete and concentrate solutes. This was also demonstrated by the urea clearance test; on the tenth day (prediuresis) it was 4 per cent of average normal and, in the subsequent three weeks, there was a slow, linear return to normal values.

Clinical recovery was complete when the patient was last seen on the forty-fifth day of observation. Laboratory indications of renal involvement were likewise absent save for the mild diminution in maximum urine concentration.

CASE II. *Acute Toxic Nephrosis from Hemolytic Transfusion Reaction ("Transfusion Kidney")*. This twenty-nine-year old soldier suffered a penetrating wound of the left leg and a severe compound comminuted fracture of the left tibia during action in November, 1944. Four months later, when he arrived in the Zone of Interior, he was still bedridden and chronically ill from an active, secondary osteomyelitis. The cardiovascular and renal systems were normal; the blood pressure averaged 136/80. The past history was non-contributory.

On March 27, 1945, he underwent a saucerization of the left tibia. A transfusion was given postoperatively to promote healing. Shortly after he had already received about 135 cc. of blood, the patient felt uneasy, complained of severe backache, vomited a watery, sanguineous fluid and had a shaking chill. The transfusion was promptly discontinued and the patient felt better. An hour later, however, there was a profuse hemorrhage through the leg cast (estimated loss of 750–1,000 cc.). Shock developed, the blood pressure fell to 70/30, and

he voided a grossly bloody urine. Although the shock state responded to therapy that included intravenous fluids, plasma and sodium bicarbonate, the patient became anuric and was transferred to the Cardiovascular-renal Section for treatment. Subsequent studies disclosed this to be an incompatible transfusion reaction; a recheck of the cross-matching revealed the donor to be in Group A (weak agglutinogens) and not in Group O as previously typed by two laboratories. The patient was in Group O.

Figure 2 summarizes the pertinent features of the fluid intake and output, blood, blood pressure and blood chemistry studies. After the initial use of parenteral fluids to combat shock and to stimulate diuresis, fluids were restricted to an intake of 650–1,350 cc. daily. Included in this intake total are indirect transfusions of whole blood, preceded by 10 cc. of 10 per cent calcium gluconate, on the second, third and fourth days. Not included in the intake is the very thick oatmeal gruel given from the fourth day on in amounts of not over 200 cc. daily. Oral fluid intake was minimal until the fourth day. Thereafter, the patient was encouraged to take an ounce of thick gruel every hour. The vomiting diminished despite the progressive renal insufficiency and the patient was happier. Because of this oral tolerance and the aggravation of vomiting by intravenous fluids, particularly by 50 per cent glucose, all parenteral fluids were discontinued after the seventh day. With the onset of diuresis, the chief guide to oral fluid intake was the patient's thirst.

The post-transfusion course was generally afebrile except for an occasional rise to 101°F. Headache, cough, mild hiccough, costovertebral tenderness, nausea and vomiting were the earliest symptoms; the latter persisted into the period of diuresis. Following the hemolytic transfusion reaction the patient voided about 300 cc., then became anuric for thirty-six hours; an output of 210 cc. (pH 5.5) was again followed by forty hours of anuria, in turn followed by severe oliguria. Urinary output increased progressively on the ninth, tenth and eleventh days until diuresis appeared from the twelfth to the twentieth day.

Neck vein distention, labored breathing, and abdominal distention appeared on the third

day of illness. The liver edge was palpable at two fingerbreadths on the fifth day and reached a maximum of four fingerbreadths on the eighth day. Hypertension was noted on the seventh day and was maximum (160/112) on the eighth day. On this day there were indications of significant fluid retention and early cardiovascular embarrassment. The patient was dyspneic on slight exertion, his face was puffy, there were scattered, crackling rales at the bases of the lungs, the heart action was forceful, P_2 was accentuated, the apical first sound was thumping, a faint apical systolic murmur was noted, the liver was enlarged to four fingerbreadths, and a portable x-ray of the chest disclosed accentuated bronchovascular markings and a delineation of the right interlobar septum.

Between the ninth and eleventh days the general condition was stationary, but with the onset of diuresis on the twelfth day there was prompt and striking improvement despite the azotemia that reached its peak on the thirteenth day (non-protein nitrogen 172 mg. per cent, urea nitrogen 150 mg. per cent) and then declined over a period of eight days. After twenty-four hours of diuresis, P_2 was no longer accentuated, the pulse was not bounding, the blood pressure fell to 146/96, the liver decreased in size, and the patient enjoyed a 1,200 calorie diet. Improvement was rapid and progressive thereafter, the hypertension disappeared after the sixteenth day, and a chest film disclosed diminution of the bronchovascular shadows and disappearance of the previously delineated interlobar septum. On completion of diuresis the extremities were notably thin, shrunken and the skin was wrinkled, indicative not only of marked fluid retention but also of a significant loss of tissue substance.

Improvement in renal function was slower, the urea nitrogen being still elevated after completion of diuresis. A normal urine concentration test (Table 1) was not obtained on the fifty-seventh day and the urea clearance test was still subnormal on the fifty-fourth day. Follow-up studies four months after the hemolytic reaction revealed complete clinical and laboratory cure. Eleven months after the acute toxic nephrosis the patient was re-examined and no abnormalities were detected in the renal or

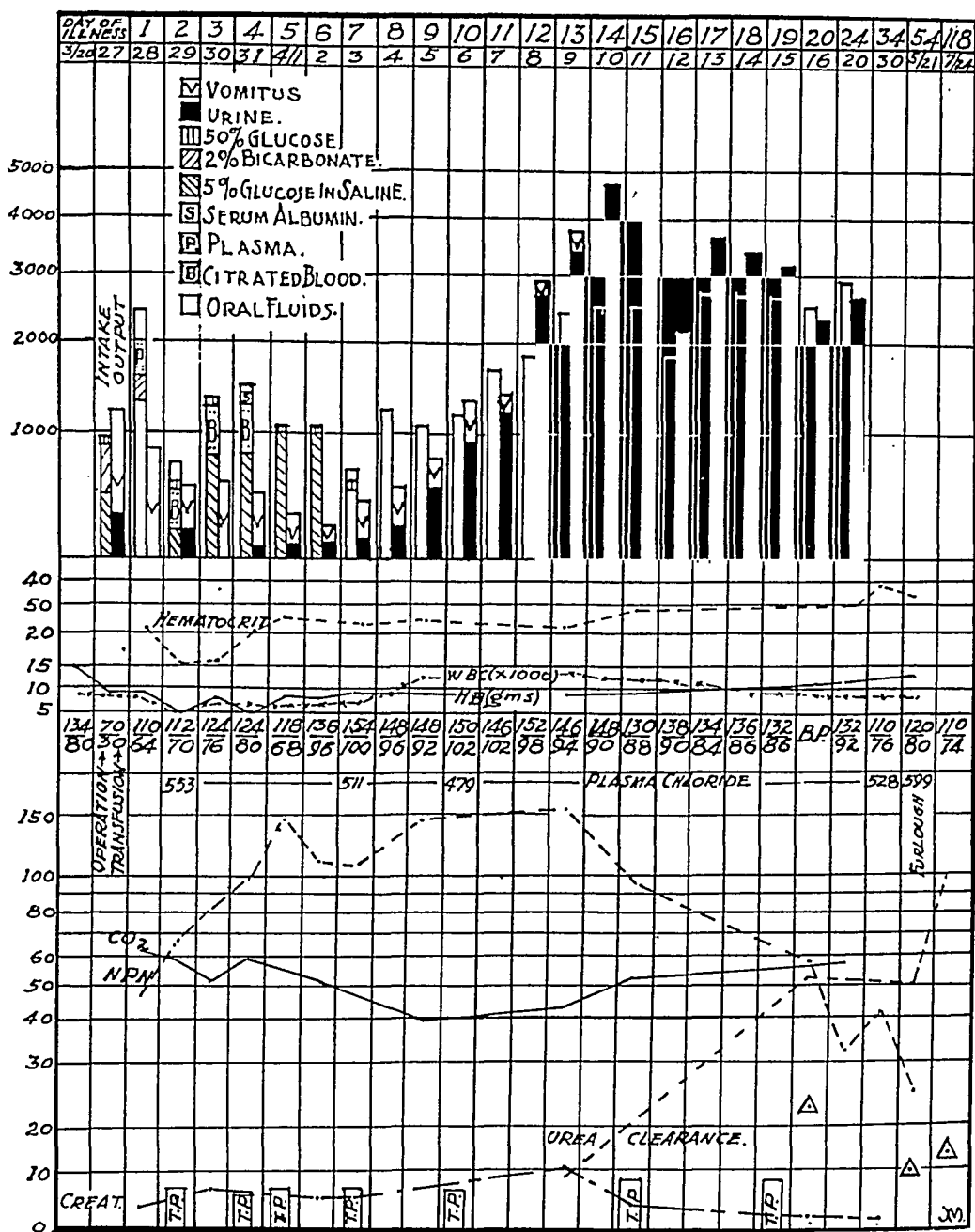


FIG. 2. Composite of intake, output, blood studies, blood pressure and blood chemistry. \overline{TP} = Total protein. ∇ = Blood urea nitrogen. Intake, output and blood chemistry charted on semi-logarithmic paper. Chlorides, non-protein nitrogen, blood urea nitrogen and creatinine recorded in mg. per cent; CO₂ in volumes per cent; total proteins in Gm. per cent; urea clearance in per cent of average normal function.

cardiac systems by clinical and laboratory studies.

Comment. This is also a typical example of acute toxic nephrosis, in this instance resulting from an incompatible transfusion reaction. Judged by the amount of incompatible blood administered, the prognosis was relatively favorable.⁶ Judged by the degree and duration of oliguria and anuria, nitrogen retention and other clinical and laboratory abnormalities, the degree of renal insufficiency was indistinguishable from reported cases with fatal termination. Severe hemorrhage and shock were additional hazardous complications. Transfusions, employed gingerly at first and more boldly later, corrected the complicating anemia but had no immediate effect on restoring renal function. Anuria and oliguria were followed by progressive azotemia, fluid retention, plethora, hepatomegaly, hypertension, cardiovascular embarrassment, and latent pulmonary edema.

After the initial use of parenteral fluids and plasma succeeded in combatting shock, but failed to maintain adequate urinary output, fluid intake was restricted. A fixed daily intake was not prescribed, but enough fluids were given to equal approximately the estimated insensible fluid loss plus that amount lost by vomiting. As occurred with Case 1, the disquieting status of the patient at the end of a week evoked a conference on therapy. No two internists or surgeons could agree on a plan for future therapy, but there was general disapproval of the unorthodox restriction of fluids and avoidance of parenteral therapy. A variety of medical and surgical procedures were individually championed. No actual change in the management was made, however, and spontaneous recovery fortunately ensued.

Calculation of the gross intake and output (Fig. 2) for the first nineteen days discloses an excess of output over intake of about 1,400 cc. At first glance, this discrepancy

might be dismissed as within the limits of error. When, however, there is included in the output the insensible loss of fluid by lung, skin and bowel (say only 250–500 cc. daily) the excess of output over intake is about 7,500–11,000 cc. Comparable figures are not available for Case 1 but the clinical impression in both cases was that the degree of water retention and diuresis exceeded that expected from the intake. Is there an internal source of this fluid and what is its significance? In both cases, although the exact weight loss is unknown, it was clinically evident at the completion of diuresis that significant weight loss, easily fifteen to twenty-five pounds, had occurred as a result of intoxication, starvation, vomiting, acidosis and fever. Destruction of this amount of tissue will liberate 5,000–10,000 cc. of intracellular fluid. Since water excretion is a fundamental impairment in acute toxic nephrosis, an occult, unsuspected fluid retention thus develops that materially aggravates the edema tendency and its complications. This endogenous source of fluid retention may account for reports of fatal heart failure and pulmonary edema developing in acute toxic nephrosis despite cautious administration of fluids.⁷

Theoretically, potassium intoxication is a possible consequence of this toxic destruction of tissue and liberation of intracellular fluids. Potassium studies were not obtained in the above two cases but there are reports of elevated potassium in crush syndrome.⁸ The elevated blood potassium in crush syndrome has been attributed to tissue breakdown in the crushed limb. In animals made anuric by ligation of the ureters or by nephrectomy, potassium poisoning is the cause of death by producing cardiac irregularity and sudden cardiac arrest.⁸

COMMENT

The close similarity in the clinical manifestations, clinical course, and laboratory

findings establish acute toxic nephrosis, of varied etiology, as a clinical syndrome. Figures 1 and 2 resemble not only each other but also other reported cases. These charts also reveal marked similarities in the duration of the oliguria-anuria and pre-diuretic phases, the onset of diuresis on the eleventh and twelfth days, the duration of the diuresis, the hypertension, the degree of azotemia and its relatively slow decline, the reduction of CO₂ combining power, the evidences of impaired tubular function, and the gradual, progressive restoration of tubular function. The urinary findings are also similar (Table I), although pigment derivatives of hemoglobin (myohemoglobin in crush syndrome) are present in "transfusion kidney" but not in carbon tetrachloride nephrosis.

The similarity in the pathology of this syndrome, especially the selective tubular damage, is evident in the following quotations:

Carbon Tetrachloride. "The anatomic basis for the clinical and renal symptoms is nephrosis characterized by distention of the spaces of Bowman with albuminous precipitate, with swelling of the lining cells, swelling and vacuolation of the cells of the proximal convoluted tubules, degeneration and necrosis of the cells of the distal convoluted tubules and those of the loops of Henle, with desquamation, and by the presence of granular, hyaline and cellular casts in the tubules, with plugging of their lumens. Concretions are present whose nature and significance are obscure."⁵

Hemolytic Transfusion Reaction. "The most characteristic postmortem findings in the patient who died as a result of transfusion of incompatible blood are seen in the kidneys. They are usually somewhat swollen, but otherwise present no pathognomonic gross lesions. Microscopically, the most striking change consists in the presence, within the renal tubules, of pigmented casts, consisting of hemoglobin or the degradation products

of hemoglobin. Characteristically, these casts occur only in certain portions of the tubules, namely, the ascending loops of Henle, the distal convoluted tubules and the collecting tubules. Furthermore, the casts are not diffusely but irregularly distributed, and the majority of the tubules may not be involved. Less conspicuous, but perhaps more important, are degenerative or even necrotic changes in the tubular epithelium of relatively short segments of the ascending loops of Henle and the distal tubules. In the neighborhood of the more severely damaged segments, the interstitial tissue often exhibits an inflammatory reaction with small cells predominating. The changes in the tubules and their supporting stroma are usually most evident in the zone between the cortex and the medulla. In contrast to damage affecting the lower portion of the nephron, the upper portion, that is, the glomeruli and the proximal tubules, are usually normal."⁹

Crush Syndrome. "There is no significant change in the glomerular capillaries. The capsular space and the lumen of the first convoluted tubules contain a variable but sometimes considerable amount of amorphous and granular debris . . . The most striking changes are found in the ascending loop of Henle and the second convoluted tubule . . . The epithelium lining this part of a considerable number of nephrons shows clear evidence of necrosis. This change is particularly intense in microscopic foci usually situated in the boundary zone. In these foci the tubular wall is weakened and occasionally ruptured and there are areas of tubular collapse with early fibroblastic and histiocytic proliferation in the interstitial tissue. Epithelial regeneration in this part of the nephron (second convoluted tubule, boundary zone) is clearly present in most cases surviving the seventh day . . . It is in this part of the nephron and in the collecting tubules that the "pigment casts" (myohemoglobin or a simple derivative) so

typical of the condition are seen. In the majority of cases these casts are numerous and conspicuous and become larger and longer as the collecting tubule is reached. In some cases they are relatively scanty.”⁸

Analogous experimental changes, that is, severe selective tubular damage to ascending loops of Henle and the second tubules are seen in the poisoning produced by lithium monourate (rabbit),¹⁰ phosphate nephritis of rats,¹⁰ and carbon tetrachloride poisoning in cats.¹¹

The studies of the pathology of human acute toxic nephrosis have a common failing in that the specimens are obtained at a stage of fluid retention, as a result not only of oliguria-anuria but also at a stage when oliguria has persisted “in spite of the administration of large volumes of fluid.” May not the kidney engorgement, in part at least, reflect the retained fluids and increased blood volume that are responsible for an analogous enlargement of the liver? Solution of this and similar questions is of practical importance since therapy has been predicated on the findings at autopsy.

The pathology of acute toxic nephrosis likewise fails to uncover the pathogenesis of this syndrome. Is the acute renal insufficiency the result of vasoconstriction, edema, tubular blockage, tubular necrosis, nephrotoxic effect, a combination of these effects, or is the cause perhaps still unknown? Is the mechanism that initiates this anuria the same as the sustaining mechanism? How does recovery take place? These are questions of therapeutic importance, for the obstructive theory of acute toxic nephrosis has led to intravenous injections of large amounts of fluid and alkali; the edema theory, to late decapsulation; and the theory of increased intrarenal pressure² to immediate decapsulation as an emergency surgical procedure of the same urgency as appendectomy.

The obstructive theory (blockage of

renal tubules) is being generally abandoned.^{2,6,8,9,10,12} Bywaters¹³ pointed out that if the anuria of crush syndrome were due to tubular blockage, any urine secreted must be derived from unobstructed tubules and should be normal; actually, the urine in his cases was little more than a glomerular filtrate. Dunn¹⁰ compared the concentration of urea in blood and urine in crush syndrome and found extreme impairment of concentration power, indicative of severe tubular damage. Cases I and II, as indicated previously, revealed severe tubular damage in both the pre- and postdiuretic phase. Awareness of the pathology of the allied carbon tetrachloride nephrosis might have prevented the therapeutic emphasis on blockage of tubules by hemoglobin and its derivatives by the students of ‘transfusion kidney.’ Therefore, the theoretical indications for “flushing” the kidneys to overcome a block, using large amounts of fluids, are no longer tenable.

Bilateral renal decapsulation, to relieve “acute congestion and swelling of the kidneys,” has fallen into disfavor. Unilateral renal decapsulation still has its advocates.^{14,15} Figure 3 was prepared from the material available in articles recommending unilateral decapsulation. Comparison of the urinary output in Figures 1, 2 and 3 reveals a very similar course. It also reveals that decapsulation was performed in the pre-diuretic period and that there was an appreciable delay between decapsulation and the diuresis. The patients represented in Figure 3 were also treated with daily intravenous infusions of 3,000 or more cc. for prolonged periods.

Johan T. Peters² proposes that “the primary cause of the oliguria or anuria is a decrease of the effective filtration pressure as a result of an increased intrarenal pressure.” This increased intrarenal pressure may result from dilatation of tubules, interstitial edema, inflammatory exudate and swelling of the

tubular cells. Employing an ingenious mechanical device ("artificial nephron") that imitates the pressure relationships and fluid output of the kidney, Peters finds that an increase of a few millimeters of mercury in the intrarenal pressure may cause

on autopsy or decapsulation have been previously stated. A more serious criticism is that the intrarenal pressure theory fails to explain the spontaneous diuresis that occurs on the eleventh or twelfth day of illness at a time when fluid retention in the skin, liver,

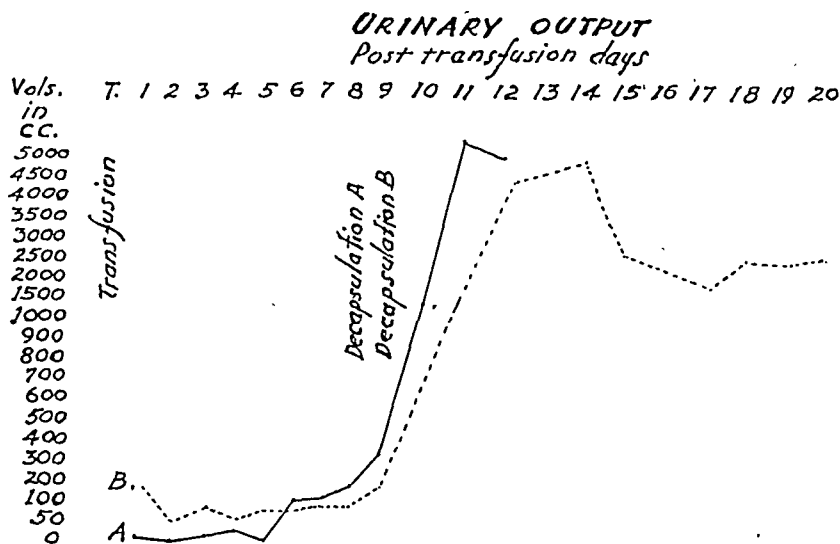


FIG. 3. Data modeled after reports of two cases^{14,15} of "successful" unilateral decapsulation.

"oliguria" or "anuria," whereas a slight decrease of an increased intrarenal pressure (analogous to decapsulation *in vivo*) promptly restores the normal "urinary output." From these and other considerations, Peters concludes that "emergency decapsulation in severe cases associated with the syndrome is more urgent than appendectomy in acute appendicitis." The factor of increased intrarenal pressure deserves careful consideration; the therapeutic principle derived from this theory can, and should be, tested in animals rendered acutely nephrotic by carbon tetrachloride, incompatible transfusion, or crushing of an extremity.

There are several objections to the theory of increased intrarenal pressure as the sole or main factor in acute toxic nephrosis. There is no evidence that swelling of the kidneys precedes the initial oliguria. Cases are reported in which the kidney lesion is insignificant.¹⁶ The objections to the interpretation of the swelling of the kidneys noted

lungs and kidneys is maximum. The theory of increased intrarenal pressure would logically infer that diuresis is least possible at the height of renal swelling.

Discovery of the mechanism of spontaneous diuresis might result in specific therapeutic measures. A relationship worthy of consideration is the aspect of tubular regeneration. In acute toxic nephrosis the basement membrane is usually intact and tubular regeneration is rapid, being first noted on the third day after injury and resulting in complete reclothing of the tubules by epithelium by the fourteenth day.⁸ The time relationship of this regeneration to diuresis is suggestive, as is the manner of recovery of tubular function. Were this the mechanism, treatment and prognosis would be concerned with tubular regeneration and the ability to tide the patient over until regeneration has occurred.

With this background of clinical observations, pathology, pathogenesis, and re-

covery mechanisms, it is clear that specific therapy is not now available. Since clinical recovery is initiated by diuresis (although anatomical damage and impaired tubular function persist for an appreciable time thereafter), any measure that would produce diuresis would be a satisfactory therapy. Although a variety of measures have been reported successful in isolated cases, critical evaluation fails to disclose any known successful therapy in a significant number of cases.^{6,9} These measures include isotonic or hypertonic fluids ranging from "adequate" to "massive," intravenous sodium bicarbonate or $\frac{1}{6}$ molar sodium lactate, intravenous sodium sulfate, transfusion of compatible blood and plasma, phlebotomy, decapsulation of kidney, irrigation of renal pelves, spinal anesthesia, splanchnic block, diathermy to kidney regions, x-ray irradiation of kidney regions and aceyltbetamethylcholine.

Since there is no specific therapy and no reliable method of initiating diuresis, attention is focussed on measures to aid spontaneous recovery. This approach is aided by analyzing the causes of death in acute toxic nephrosis. Of course, in some of the cases, the exposure to the intoxicant is so great and the damage to various organs is so widespread that the downhill course is rapid and relentless due to generalized toxic effects rather than to isolated renal insufficiency. When, however, the acute injury is survived and the course is that of protracted renal insufficiency for seven to ten days, death is commonly reported as "of uremia." The observations and comments in Cases I and II indicate that the degree and duration of the azotemia are not the prime determinants of the illness. Death from transfusion kidney, in four to ten days,⁹ and from the crush syndrome, seven days on the average,⁸ occurs too soon to be primarily "uremic." A review of unselected fatal cases reveals some interesting observations. (Table II.) Death

occurred between the third and thirteenth day, 7.7 days on the average. Although the authors were not particularly concerned with water metabolism and cardiovascular complications, there are clinical and pathological evidences of such effects in nine of the cases. In one instance,¹⁷ (Case I) generalized edema appeared on the second day after the transfusion reaction despite an intake of 2,000 cc. daily. In another patient (Case IV) generalized edema was present on the third day after the reaction and death from pulmonary edema occurred on the following day when the maximum NPN was 112 mg. per cent. One death occurred on the third day; although oliguria was present, the presumptive cause of death in this case was overwhelming intoxication.

These observations from the literature coincide with the observations in the two reported cases that water retention, circulatory overload, cardiac embarrassment and pulmonary edema weigh heavily in the outcome. The puffy appearance, neck vein distention, early onset and progression of liver enlargement, and accentuated pulmonary second sound are clinical manifestations of the embarrassing plethora; recent investigations disclose a circulating blood volume "far above the values for normal" in transfusion anuria.⁹ The endogenous source of fluid retention plays a significant and hitherto unappreciated rôle in this train of events. The similarities of the two case reports have been commented on previously; there is one important difference. Case I, on a daily intake of about 2,600 cc. for six days, developed anasarca, cardiac dilatation, congestive failure and pulmonary edema despite restriction of fluids after the sixth day. His recovery despite these complications is a tribute to his youth and sturdy cardiovascular system. (These attributes cannot be predicated in other cases.) Case II, on the contrary, did not progress to congestive failure and pulmonary edema but, even

on an average fluid intake of 1,000 cc. daily, did develop generalized edema, hepatomegaly, probable early cardiac dilatation, cardiac embarrassment, and latent pulmonary edema. In this bedridden, wounded, chronically ill patient the additional burden

A final consideration bearing on the employment of fluids, salts and alkali in acute toxic nephrosis is the appreciation of the role of the kidney in the regulation of water balance, blood volume, electrolytes and acid-base equilibrium. Tubular function,

TABLE II
DATA RELATING TO DATE AND CAUSE OF DEATH IN 13 UNSELECTED CASES OF ACUTE TOXIC NEPHROSIS

Etiology	Fluids	Clinical Manifestations	Day of Death	Autopsy
Carbon Tetrachloride Perry ¹⁸ Case I.	?	Marked congestive failure	10th	Pleural effusion. Marked pulmonary congestion
Case II.	?	Exaggerated heart sounds Soft tissue edema	5th	Intense congestion of lungs. Extensive hepatic damage
Smetana ⁵ Case I.	"Large infusions"	Ascites	10th	Ascites
Case III.	?	Heart enlarged to left and right Gallop rhythm—No peripheral edema, rapid pulmonary edema	8th	Marked edema of lungs
Hemolytic Reaction Daniels ¹⁷ Case I.	2,000 cc. daily	Generalized edema after 48 hrs.	5th	Congestion and edema of lungs
Case II.	3,000–3,700 cc. daily	Generalized edema	8th	"Considerable" congestion of lungs
Case III.	"Large amounts"	Generalized edema "Death with pulmonary edema"	13th	Autopsy limited to abdomen
Case IV.	"Massive quantities"	Generalized edema after 72 hrs	5th	Edematous lungs
Case X.	Large amounts of fluid and alkali	Maximum NPN 85 mg. %	3rd	No autopsy
Case XI.	?	?	9th	No autopsy
Case XII.	3,000 cc. daily	Râles at bases 2nd–3rd day	6th	No autopsy
Crush Syndrome Dunn ¹⁰ Case I.	510–3,630 cc. daily (av. 2,000)	Gross edema both legs and chest wall (?trauma)	9th	1,500 cc fluid in each pleural cavity; both lungs edematous
Case II.	?	?	7th	Slight dilatation right heart

of cardiac and pulmonary complications probably would not have been tolerated. The early appearance of generalized edema and plethora would indicate an excess of available fluid and would argue against further administration of fluid. Furthermore, excess fluids adversely affect the concentration of electrolytes in the extracellular fluid.¹⁹ Restriction of fluids does not interfere with spontaneous diuresis when the recovery mechanism becomes effective. (Cases I and II.)

by virtue of absorption and secretion, plays a predominant rôle in this regulatory mechanism. The value of fluids, salt and alkali in toxemia and acidosis is not denied, provided kidney function is adequate. When, however, this regulating function is severely impaired or lost, as results from the marked tubular dysfunction of acute toxic nephrosis, the effects of fluids, salt or alkali are completely unpredictable and potentially harmful. If, as is commonly proposed for hemolytic transfusion reaction, twelve to

fifteen Gm. of sodium bicarbonate are routinely administered daily, it is uncertain whether there will be any change in the CO_2 combining power or whether alkalosis will ensue. The effects of the sodium ion component of the alkali will certainly result in aggravation of water retention and edema. It is, therefore, proposed: Do not treat the blood chemistry. Restoration of tubular function will, of itself, correct hypochloremia, acidosis and increased blood volume. (Cases I and II.) In an occasional case the depression of chlorides and CO_2 combining power may reach levels that are hazardous *per se*; in such occasional instances, the cautious administration of salt and alkali may be ventured under constant clinical and chemical guidance.

This detailed consideration of the problem of fluid management in acute toxic nephrosis is necessitated by the almost universal acceptance in practice of the advice in text books and articles to treat such patients with fluids, usually intravenously. The amount of fluids recommended ranges from "large volumes" to "adequate." It is not uncommon to find in the same article a recommendation that fluids be "forced" and that pulmonary edema be guarded against. One plan of treatment of post-hemolytic transfusion reaction²⁰ that recently has been widely circulated recommends: "For prophylaxis . . . if sodium bicarbonate solution is used by mouth or vein, 1,500 cc. of isotonic (one-sixth molar) sodium bicarbonate solution should be given daily in divided doses. If sodium lactate solution (one-sixth molar) is used, the dosages are identical. For therapeutic use with already developed anuria, these dosages may not be sufficient and can be safely tripled the first day and thereafter reduced to the prophylactic dose. Other fluid should be given in addition to the alkaline solution, and in general for every unit of bicarbonate or lactate solution given, an equal quantity

of isotonic solution of sodium chloride may be administered." Interpreted literally, this means that the anuric patient may safely receive 4,500 cc. of alkaline solution and 4,500 cc. of isotonic sodium chloride solution on the first day and 1,500 cc. of each solution daily thereafter. That even half this amount is not safe is gaining recent recognition. For example: "Abundant evidence has appeared that not infrequently patients with injury of kidney tubules are harmed rather than helped by persistent efforts to secure diuresis by maintenance of fluid intake in excess of fluid output . . . pulmonary edema is an important cause of death (in hemolytic transfusion reaction*). Thereafter (i.e., after the first twenty-four hours in which an excess of 3,000 cc. is allowed over intake*) fluids are given strictly in accordance with demands of fluid loss."²¹

Even when the dangers of excessive fluid and salt are well recognized and the "greatest stress" is placed on proper regulation of salt and fluid, there is reluctance to accept the logical conclusion: "The oliguric patients (from transfusion reaction*) very often show an increased plasma volume even on a moderately restricted fluid intake . . . It is difficult to state how much fluid should be administered . . . It may be well to administer a fairly large volume (4,000 cc.*) of fluid during the first twenty-four hours in an attempt to promote diuresis. Subsequently it will ordinarily be sufficient to limit parenteral fluids to one liter of 0.85 per cent solution of sodium chloride and an additional liter of 5 per cent dextrose in distilled water. It must be remembered that the quantity of sodium must be limited as well as the total volume of fluid."⁹ Case I illustrates that fluid administration of this degree may result in congestive failure and pulmonary edema; Case II, who received about one-half the recommended quantity

* Phrases in parentheses inserted by author.

of fluid, developed significant fluid retention and cardiac embarrassment. It is probable that the stumbling block in most plans of fluid management is the failure to consider the endogenous production and retention of fluid.

In a review, admittedly incomplete, of the literature there was not encountered any detailed case report in which treatment consisted of strict limitation of fluids. Nor were any cases of acute toxic nephrosis encountered that were suffering from dehydration. Peters² does recommend restriction of fluids but this recommendation is not amplified. Styron and Leadbetter²² caution against the "aimless administration of fluids" and advise that "the administration of fluids should be governed by the rate of renal excretion and by the level of the non-protein nitrogen and chloride."

Since manifest edema in acute toxic nephrosis represents a significant degree of fluid retention, probable increased circulating blood volume and circulatory overload, the author recommends as a general principle that fluids be restricted below the amount that will produce manifest edema. To prevent an excess of fluid retention over fluid output it is necessary to know not only the urinary output and fluid loss by other channels but also the amount of fluid liberated from the tissues. Since the latter is undeterminable, it is preferable to err on the side of restriction. The approximate daily sodium chloride need of the resting normal adult is satisfied by about 700 cc. of physiologic saline solution.²³ This amount of salt and fluid can be used as the basic intake that may be increased or decreased in accordance with the measured loss of fluid and salt or with evidences of dehydration or mounting fluid retention. Diuresis in this syndrome is not enhanced by intravenous fluids; the route of administration is a matter of clinical judgment. In Case I, vomiting was diminished by restricting oral intake and sub-

stituting the intravenous route; the opposite was true for Case II. It probably requires reiteration that intelligent handling of this problem necessitates careful determination of intake and output. Daily weighing, if possible, may be helpful although the weight may remain stationary as fluid retention counterbalances destruction of tissue. Evidences of fluid retention, plethora and circulatory overload are to be sought for repeatedly not only in the skin but also in venous distention, enlargement of the liver, alteration in heart sounds, particularly the pulmonic second sound, height of the blood pressure and pulmonary congestion.

Carbohydrate is indicated. It may be given in a concentration of 5 to 10 per cent intravenously; greater concentrations may be attempted but should be promptly abandoned if not tolerated. If oral carbohydrates are tolerated (Case II), thick gruel with sugar, jams, bananas, and other high carbohydrate foods may be tried. An adequate total caloric intake is a lesser problem in this disorder of limited duration. Consideration must be given to the amount of fluid produced in the metabolism of any ingested food; this fluid will also be retained in the body.

The varied etiology and complications of this syndrome, along with the frequent involvement of other organs or systems by the intoxicating agent, are a challenge to therapeutic ingenuity and to the principle of avoiding overtreatment. The recommended plan of restriction of fluids does not apply to shock, which may be present initially. Shock requires prompt, energetic treatment, preferably with blood or plasma. Significant blood loss, from hemorrhage or blood destruction, is to be corrected by transfusion of compatible blood. Clinical observations and animal experiments are cited²⁴ to the effect that immediate transfusion of compatible blood is beneficial in hemolytic transfusion reaction. (Corroborative experi-

ments are indicated in experimental carbon tetrachloride nephrosis as well. The basic unity of the clinical and pathological findings in acute toxic nephrosis would indicate that successful basic therapy would be valuable in this syndrome, whatever the initiating agent may be.) Absolute rest, mental and physical, is promoted by reassurance and sedation (avoid sodium salts in sedation); skilled nursing care is invaluable. Associated liver damage may require therapeutic consideration, and penicillin may be necessary for a complicating pneumonia or infection. The value of repeated administration of intravenous calcium gluconate (10 cc. of 10 per cent solution, several times daily) deserves further trial if liver damage is present.⁴ Hemorrhagic tendency may respond to parenteral vitamin K. (Case 1.) Dietary management must be flexible and supportive treatment may be required for some time after successful initiation of diuresis. The original condition prior to the acute toxic nephrosis, as pregnancy, wounds or other surgical conditions, may have its own therapeutic problems that require integration with the management of the renal lesion. Bandaging or freezing of the crushed limb, to retard the liberation of "nephrotoxins," are advocated in crush syndrome.²

Prevention is the most important aspect of the problem of circulatory overload, cardiac failure and pulmonary edema. In the literature, the feature of cardiac failure receives negligible attention although Riddell²⁵ believes it to be the commonest cause of fatality following incompatible blood transfusion. Cardiac failure is apt to be unexpectedly abrupt (Case 1), may occur quite early, and is frequently masked by the pre-existent fluid retention and generalized toxic manifestations. Early, slow, digitalization would seem to be indicated although it was not employed in the two case histories reported. Digitalis overdosage is to be care-

fully guarded against in view of the impaired renal excretion. Venesection of 500 or more cc. may be helpful in relieving circulatory overload, pulmonary edema, and episodes of hypertensive encephalopathy; the latter may require morphine and spinal puncture as well. A purely speculative therapeutic suggestion is the possibility of exsanguination transfusion in the case that progresses unfavorably despite all measures. Removal of 2,500 to 3,000 cc. of the patient's blood, and replacement by an amount of whole blood that is 500 to 700 cc. less than was removed, may aid in tiding the patient over the critical period. The known frequency of transfusion reactions in kidney diseases makes this an admittedly desperate measure.

A very recent and intriguing publication²⁶ proposes the use of the peritoneum as a dialyzing membrane for extrarenal excretion, to tide the patient over until renal function is spontaneously restored. Inlet and outlet tubes are introduced with "minimal surgical trauma" into the peritoneal cavity and the cavity is irrigated daily by 20 to 35 liters of specially prepared Tyrode's solution. Crystalloids are thus removed from the blood with an "efficiency adequate to substitute for renal function." The authors report the successful use of this method in a fifty-one year old man who was expected to succumb to "uremia." They further remark that this method "eliminates the need of routine intravenous fluid therapy. It is unlikely that unrestricted water administration speeds the recovery of kidney function." This technic of peritoneal irrigation should also be assessed by trial in experimental acute toxic nephrosis produced by different agents. Human cases are too occasional, too sick and too complicated to lend themselves to controlled studies. More frequent use of animal experimentation is urged to determine the efficacy of the various therapeutic measures recommended in acute toxic ne-

phrosis; including the present proposal of adjusted fluid restriction as the basic therapy until spontaneous recovery ensues.

SUMMARY

Acute toxic nephrosis is a distinctive clinical syndrome, with a striking uniformity of clinical manifestations, clinical course, laboratory findings, and pathology despite a varied etiology. This discussion is restricted to the acute renal injury resulting from carbon tetrachloride poisoning, hemolytic transfusion reaction and crush syndrome. The disorder usually terminates either in death or in spontaneous, complete recovery within two weeks after the initial injury.

The details of a case of carbon tetrachloride poisoning (Case I) and a case of hemolytic transfusion reaction (Case II) are presented to illustrate the clinical and laboratory features of this syndrome. These cases are not presented as models of therapy. Rather, they reflect the lack of any specific therapy, the problems of management, and the fallacy of imputing therapeutic value to medical and surgical measures that are currently advocated. Both cases recovered spontaneously, diuresis occurring on the eleventh and twelfth day of illness, respectively. Recovery was substantially complete.

The acute renal insufficiency of this syndrome is manifested by severe impairment of excretion of water and marked depression of tubular function. The acute, initial and persistent oliguria-anuria is followed, at times very rapidly, by fluid retention, increased circulating blood volume, circulatory overload, cardiac strain, rapid cardiac failure and pulmonary edema. Azotemia and hypertension are of subsidiary importance. Both cases demonstrate clearly that the striking clinical improvement that occurred promptly after the onset of diuresis resulted from the release of retained fluid and the relief of circulatory overload. This

improvement bore no relationship to the degree of azotemia or hypertension.

The generally accepted therapy of intravenous fluids in acute toxic nephrosis is challenged as being harmful as well as ineffective. Intravenous fluids, ranging from "adequate" to "massive," consistently fail to improve urinary output. The cumulative harm of excess of intake over output lies not only in aggravation of the consequences of fluid retention but also in the fact that this harm is potentiated by another, hitherto unrecognized, source of fluid retention, endogenous fluid derived from tissue destruction. Restriction of fluids, on the contrary, does not hinder the diuresis that heralds recovery. Death in acute toxic nephrosis usually occurs in from seven to eight days. Uremia is not the usual cause of death. The cardiovascular complications deserve the greater emphasis and wider recognition.

Selective tubular damage is the outstanding pathological feature of this syndrome. The objections to the therapeutic implications drawn from the pathological studies in this syndrome are stated. The pathogenesis of acute toxic nephrosis still remains obscure and the mechanism of recovery is unknown. Tubular regeneration and diuresis parallel each other although evidences of tubular dysfunction persist for months after clinical recovery.

None of the numerous medical and surgical procedures advocated in the treatment of acute toxic nephrosis has been found effective in a significant number of cases. The basic approach to the present treatment of this syndrome should therefore be the selection of a plan of management that will tide the patient over the acute renal injury and that will favor spontaneous recovery. It is believed that fluid restriction is the keystone of this plan of management. Fluids should be restricted below the amount that will produce manifest edema or aggravation of circulatory overload. An initial daily intake

of 700 cc. of physiological saline, not necessarily intravenously, is advocated; this amount should be increased or decreased as clinical observations indicate. Other features of management and various therapeutic adjuvants are discussed.

Acute toxic nephrosis can be induced experimentally by a variety of agents. Such experiments are urged to determine the efficacy of proposed therapeutic procedures and to assess the value of plans of management.

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Enhancement of Penicillin Blood Levels in Man by Means of a New Compound, Caronamide

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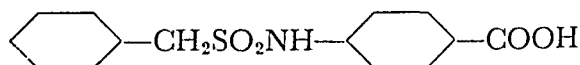
THE efficacy of penicillin as a therapeutic agent is impaired by its rapid excretion in the urine, which prevents the attainment and maintenance of high concentrations in the plasma. Relatively large doses must be administered in order to obtain detectable concentrations of penicillin in the blood stream, and massive doses of penicillin heretofore have been necessary if higher plasma concentrations are required.

The primary objective of penicillin therapy is the maintenance of therapeutic concentrations of the drug in body tissues, and it is assumed that the higher the concentration of penicillin in the plasma, the higher will be the concentration in the tissues. The commonly accepted minimal effective therapeutic level is 0.03 unit of penicillin per cc. of plasma,¹ but certain disease conditions, specifically subacute bacterial endocarditis and osteomyelitis may require much higher levels for curative effects.

Attempts to obtain high plasma concentrations (high tissue concentrations) of penicillin include: (1) increase in the dosage; (2) more frequent administration at shorter intervals; (3) variation in the route of administration; (4) attempts to slow the rate of absorption from the site of injection

and (5) partial inhibition of the renal excretion of penicillin.

This report will describe a new approach to the problem of inhibition of excretion of penicillin by the kidneys by utilizing to advantage the properties and characteristics of a new compound, caronamide, which is a white, crystalline powder with the following structural formula:



Approximately 80 per cent of the penicillin in the urine is excreted by the renal tubules, while only 20 per cent of the total urinary penicillin is eliminated by glomerular filtration.² Any agent, therefore, which is capable of suppressing the tubular excretion of penicillin without toxic manifestations should be of value in raising the level of penicillin in the plasma.

The radio-opaque medium, diodrast, frequently employed in urography and also used for determining the functional capacity of the renal tubules, is capable of suppressing the tubular excretion of penicillin.³ Sodium para-aminohippurate (PAH), which is also used frequently to determine renal function, will likewise suppress excretion of penicillin by the kidney tubules.⁴ In other words, these two substances, both of which

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are excreted by the renal tubules, will inhibit the excretion of a third substance, penicillin. The continuous intravenous administration of very large amounts of either diodrast or PAH is necessary, however, and these substances are not practical for routine use.

It has been found that a new compound, 4'-carboxyphenylmethanesulfonamide ('Staticin' caronamide*) is capable of producing reversible inhibition of penicillin excretion by the renal tubules. Caronamide is administered orally in doses of from 1.5 to 2.0 Gm. every three hours, or from 3.0 to 4.0 Gm. every four hours, and has been found to possess a low order of toxicity. It is believed that caronamide inhibits the tubular excretion of penicillin by means of "substrate competition."⁵

Diodrast, PAH and penicillin appear to be excreted through the renal tubules by the same specific transport mechanism. The excretion of penicillin is suppressed by either diodrast or by PAH whenever one or the other of these compounds is present in the blood in very large amounts. The suppression of tubular elimination of penicillin in such cases may be considered to be on the basis of "mass action." In other words, maintenance of a high plasma concentration of either diodrast or PAH will saturate the transport mechanism for penicillin and thus suppress tubular elimination of this antibiotic.

The action of the new drug, caronamide, however, is thought to be based on an enzyme-substrate competition between penicillin and caronamide, since the latter is refractory to excretion by that enzyme-transport mechanism. When caronamide is administered either orally or parenterally, experimental studies have demonstrated that this new drug will suppress the tubular excretion of penicillin by whatever route

the antibiotic is given.⁶ Caronamide differs from PAH fundamentally in its mode of action since it is eliminated from the body only by glomerular filtration. This new compound, acting as a substrate, presumably "combines" with an enzyme which is thought to be required for excretion of penicillin by the renal tubules. The enzyme-transport mechanism for tubular excretion of penicillin is thus temporarily suppressed or inhibited by the presence of caronamide in the blood stream, resulting in elevation and prolongation of penicillin blood levels.

The mode of action of caronamide relates to the selective inhibition of the essential component of that transport mechanism which is required for the tubular excretion of penicillin.⁷ That this process is reversible upon withdrawal of caronamide is demonstrated by the fact that the enzyme is released for resumption of its normal transport function and, following elimination of caronamide by the kidney glomeruli, penicillin is promptly excreted by the tubules in accordance with its normal pattern of renal elimination. This new compound exerts no action, at any time, on the glomerular filtration of penicillin, which continues uninhibited; nor does caronamide appear to damage the renal tubular epithelium where its inhibitory action is exerted.

Extensive laboratory investigation of the physiologic, pharmacologic, toxicologic and bacteriologic properties of caronamide seemed to justify clinical application of this new compound.⁸ Accordingly, preliminary clinical studies were undertaken at The Pennsylvania Hospital, in Philadelphia, from September 1 to November 15, 1946.

Penicillin and caronamide were given by oral administration simultaneously, every four hours, to a group of six afebrile patients for a period of six consecutive days. Penicillin was given by intramuscular injection and caronamide by mouth to an additional

* 'Staticin' is the proprietary name, caronamide the non-proprietary name for 4'-carboxyphenylmethanesulfonamide, supplied by Sharp & Dohme, Inc., Philadelphia, Pa.

five patients. The effect of caronamide by mouth on penicillin in beeswax and oil was studied in three other patients. Hospital routine was not altered in any way during the period of this clinical study; fluids were taken freely, diet was unrestricted, no

which the administration of penicillin was supplemented by oral caronamide (the drug phase). This, in turn, was followed by a third period when penicillin only was administered (the post-drug control phase). Thus, each patient was under observation

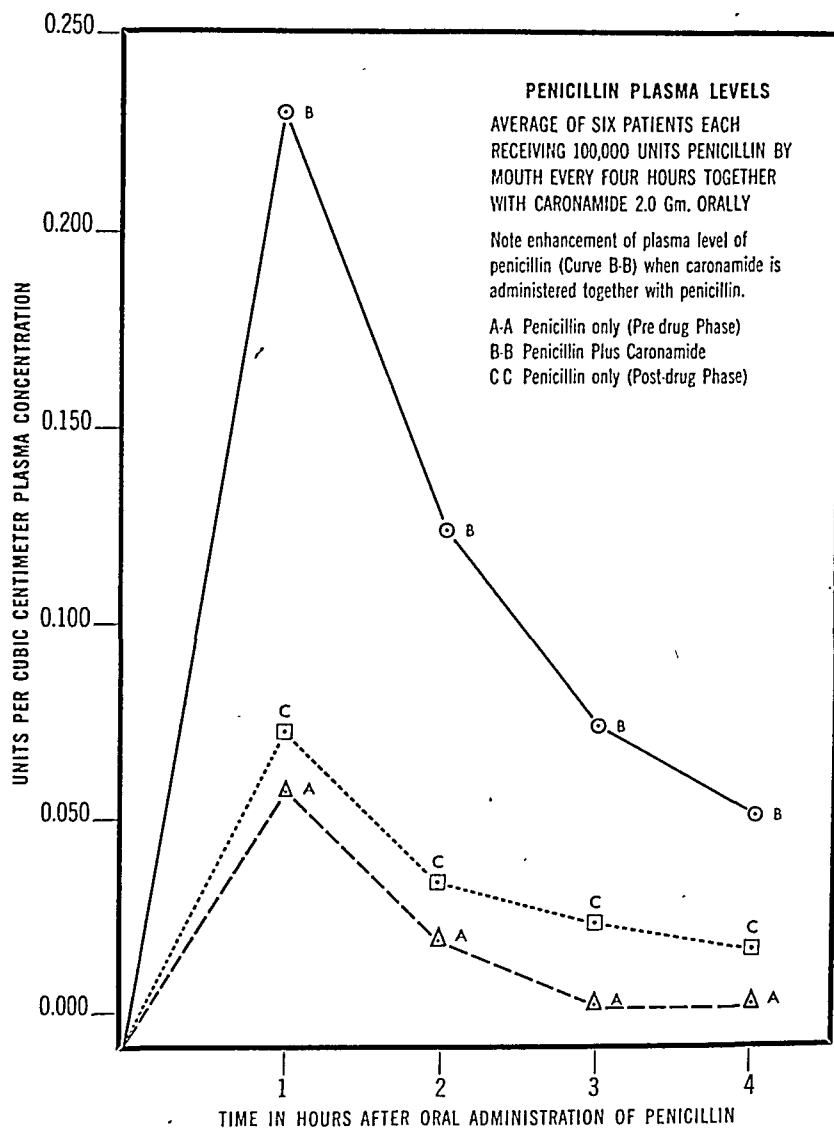


FIG. 1.

antacids were used and no additional measures were employed to enhance penicillin levels other than the administration of caronamide by mouth.

Each patient served as his own control. During the pre-drug control phase of forty-eight hours the patient received penicillin only. This was followed by a period during

during each phase of this clinical experiment to permit equilibration of penicillin alone and/or penicillin plus caronamide in the body tissues. Blood specimens for penicillin assay were drawn at appropriate, comparable times during each phase of this study to provide data concerning plasma concentrations: one, two, three and four hours

following the administration of penicillin and/or penicillin plus caronamide.

Of the six patients who received penicillin by mouth in doses of 100,000 units at four-hour intervals, two showed remarkable

caronamide was administered concomitantly, while one patient failed to demonstrate any detectable level of penicillin in the plasma before, during or after the administration of penicillin with or without caronamide.

A composite curve demonstrating the relative increase in plasma levels of penicillin is presented in Figure 1. Values from which this curve was obtained are given in Table 1.

In the five patients who received intramuscular penicillin and oral caronamide the same general plan of study was followed. The enhancement of penicillin levels by oral administration of caronamide averaged 5.7 times the penicillin plasma levels when caronamide was not administered. From this study it was found that 2.0 Gm. of oral caronamide every three or four hours produced a significant increase in the level of plasma penicillin when the antibiotic was given in aqueous solution intramuscularly.

In regard to the three patients who received penicillin in beeswax and oil by intramuscular injection, it was found that caronamide also increased the plasma concentration of the antibiotic agent, but the effect of a single orally administered dose of caronamide is lost at the end of four hours, presumably because of continued elimination of 4'-carboxyphenylmethanesulfonanilide by glomerular filtration. In other words, the major portion of a single dose of caronamide is excreted within four hours. Hence this new drug should be given by mouth at intervals of at least four hours, preferably every three hours.

These preliminary clinical studies indicate that caronamide produces an elevation of penicillin plasma concentration whether the penicillin is administered orally or intramuscularly. Further study is indicated to determine the effect of caronamide on plasma concentrations following intramuscular administration of penicillin in beeswax and oil.

TABLE I

PENICILLIN PLASMA CONCENTRATIONS (UNITS/cc)
DATA ON SIX PATIENTS RECEIVING 100,000 UNITS
ORAL PENICILLIN EVERY FOUR HOURS
Pre-drug Control Phase
Penicillin 100,000 Units by Mouth

Hours	Patients						Average
	A	B	C	D	E	F	
1	0.044	0	0.084	0.086	0.085	0.043	0.057
2	0.022	0	0.043	0.022	0	0.017
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0

Caronamide Phase
Penicillin 100,000 Units q. 4 h. by Mouth together with
Caronamide 2.0 Gm. q. 4 h., orally

Hours	Patients						Average
	A	B	C	D	E	F	
1	0.341	0	0.086	0.170	0.258	0.515	0.230
2	0.341	0	0.021	0.043	0.085	0.256	0.124
3	0.258	0	0.021	0.021	0	0.128	0.071
4	0.171	0	0	0	0	0.129	0.050

Post-drug Control Phase
Penicillin 100,000 Units by Mouth

Hours	Patients						Average
	A	B	C	D	E	F	
1	0.172	0.022	0.043	0.021	0.043	0.128	0.071
2	0.128	0	0.021	0	0	0.043	0.032
3	0.086	0	0	0	0	0.043	0.021
4	0.043	0	0.021	0	0	0.021	0.014

increases in their penicillin plasma concentrations during the period of administration of 2.0 Gm. of caronamide in tablet form every four hours. Three patients showed significantly higher levels of penicillin when

No evidence of systemic toxicity was noted in this small series of patients to whom the new compound was given. In view of the chemical structure of caronamide, however, together with extensive experience during the last twelve years with chemotherapeutic agents, some toxic manifestations in certain individuals are to be anticipated.

CONCLUSION

It has been shown that a new drug, 'Staticin' caronamide, will inhibit the renal tubular excretion of penicillin and thereby elevate the concentration of penicillin in the plasma from two- to seven-fold following the oral and/or parenteral administration of penicillin. Caronamide should be of definite clinical value in the treatment of disease conditions in which high penicillin blood levels are required.⁹

Caronamide is administered by mouth, usually in doses of 2.0 Gm. every three or four hours, concomitantly with penicillin. Given in these doses, the drug produced no evidence of renal, bone marrow or hepatic

impairment, dermatitis or drug fever in this small series of patients.

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The Syndrome of "Burning Feet" (Nutritional Melalgia) as a Manifestation of Nutritional Deficiency*

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DURING the recent war with Japan "burning feet" constituted a major problem to American forces captured by the Japanese in the Philippines. At the Bilibid Prisoner of War Hospital in Manila, the central hospital for the prisoners of war on Luzon, a commission was formed to study this condition.† The author as a member of this commission and because of his special interest in neurology carried out the detailed neurologic examinations on the patients selected for special study. The commission was constantly hampered by lack of cooperation from the Japanese authorities and when these difficulties became insurmountable a brief and unsatisfactory report was submitted to the Japanese and the study was dropped. A record of the meetings of the commission, which is of historical interest only, is in the files of the Bureau of Medicine and Surgery, U. S. Navy, Washington, D. C., among the papers salvaged from the Bilibid Hospital.

† The commission consisted of the following officers: #Comdr. T. H. Hayes, M.C., U.S.N., #Comdr. Cecil C. Welch, M.C., U.S.N., Lieut. Comdr. J. Zundell, M.C., U.S.N., Lieut. Comdr. William Silliphant, M.C., U.S.N., #Lieut. Edward Ritter, Jr., M.C., U.S.N., #Lieut. Edwin Nelson, M.C. U.S.N.R., Lieut. (j.g.) M. Glusman, M.C., U.S.N.R. The ranks indicated were those held at the time this group was formed. Names preceded by # indicate members now deceased.

The original case records of this study were unfortunately destroyed by the Japanese.

HISTORY

In the first British Burmese War (1823 to 1826), British military surgeons encountered a peculiar, disabling condition among the native Indian troops who were employed in the invasion of Burma. The British medical officers were unfamiliar with this condition and considered it a new entity. Reports dealing with the disorder appeared by Grierson¹ (1826), Playfair² (1826), Burnard³ (1829) and McKenna⁴ (1833).

Grierson, who was the first of these officers to report the condition, for want of a name simply employed the chief complaint, "a burning in the soles of the feet," in speaking of the syndrome. He observed that the condition occurred frequently after or with fever or bowel complaints but stressed the fact that it could be found apparently unconnected with any constitutional or organic disease. "It exists in various degrees of severity, from an uneasy harassing sensation of heat and tingling, to the painful extreme of burning, destructive of sleep and appetite, in the first instance, and latterly of serious injury to the general health. The sensation of heat is often experienced at the same time in the palms of the hands; and

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when severe in the feet, occasions an aching also along the tibiae as far as the knee. There is no inflammation, tension, discoloration, or visible change in the limb; the excruciating burning pain being the only symptom present; and the spot principally referred to as its seat, is the extremity of the foot, the heel and instep being less affected."

Burning feet became so important a problem among the native troops that the medical board of the Madras Presidency offered a prize of 500 rupees to the author of the best paper on the subject.⁵ The prize was won by John Grant Malcolmson and his observations were printed in 1835, by government order.

Malcolmson,⁶ who was an astute observer, attempted to differentiate burning feet from rheumatism and beriberi. He definitely drew a connection between diet and the incidence of burning feet and made the interesting observation that "in all the places in which the disease prevails rations are issued to the troops, consisting of rice, 2 ounces of ghee* (not always used), a little salt fish and spices." He claimed that the quantity of rice issued was adequate because he had seen much of the boiled rice thrown away. He concluded that "the deficiency in the food then consisted in the want of variety, of vegetables, or fresh animal food, of which almost all classes of Madras Sepoys use a certain proportion, flour, milk, and various articles with which the natives vary their diet."

Malcolmson claimed not to have seen any cases in Europeans. He noted that the involved areas were dry and did not feel hot to the touch and remarked that some patients claimed that the pain was worse at night. Malcolmson suspected that deficient nutrition and adverse climate were factors predisposing to burning feet, consequently he

made the following suggestions as to treatment: "The essential object is change of climate and a return to the usual habits of life and food of the Sepoy. . . . As the patient gains flesh, and strength, the pains and burning leave him, and he recovers without the aid of medicine." He felt that because of the practical difficulties involved in supplying extensive expeditions there was no point in recommending other types of food for the troops.

Following Malcolmson's observations burning feet received scanty and rather sporadic attention until comparatively recent times. Waring⁷ in 1860, added little to what the earlier writers had said. Collas⁸ (1861) discussed the history of burning feet, suggested the name "causalgésic" or causalgia for the condition and attempted to differentiate it from an affliction called pedionalgia or chiropodalgia which had been observed in Piedmont in 1762. LeRoy de Méricourt⁸ (1870) reviewed the work of the earlier writers and concluded that burning feet was a manifestation of beriberi.

In 1881, burning feet, under the name of "ignipedites," received brief notice from Ram,⁹ Shah¹⁰ and Naidoo¹¹ who indicated that the condition was still endemic in India. In 1904, Gerrard¹² added still another name when he described burning feet in Tamil laborers of Malaya and classified the condition under the heading "erythromelalgia tropica." Gerrard was impressed by the resemblance of the pain in burning feet to that in erythromelalgia. Redness, however, is characteristic of the painful limbs in erythromelalgia and S. Weir Mitchell¹³ indicated this when he described and named erythromelalgia. Gerrard's patients lacked redness but his explanation was that this feature was obscured to some degree by the dark skins of his native patients.

Beginning in 1927, there was something of a revival of interest in burning feet. La-

* Ghee is a specially prepared type of butter used by the Hindus. It is derived from cow's milk or water buffalo milk.

bernadie¹⁴ (1927) discussed the condition and claimed it was due to a non-specific polyneuritis. Dugdale¹⁵ (1928), Galloway¹⁶ (1928), Coope¹⁷ (1928) and Morgan¹⁸ (1929) reported the condition in laborers on Malayan estates, while Sharples¹⁹ (1929) described the same manifestations in the South American sugar plantations of British Guiana. The estate and plantation physicians attempted to link the condition to dietary deficiencies in the coolie laborers.

Burning feet appeared in Europe during the Spanish Civil War of 1936 to 1939. Peraita²⁰ referred to it as the "paresthetic-causalgic syndrome" and he discussed at length the appearance of this condition as it developed in association with malnutrition in Madrid in 1937 and 1938. He differentiated it from beriberi and from his results with therapy claimed that the syndrome was due to the deficiency of some factor present in yeast.

In the past year burning feet has again attracted notice. Gopalan²¹ (1946), working in India, described the condition and studied the effects of therapy in a series of patients. He obtained striking results with pantothenic acid. Because of its significance, Gopalan's work will be referred to in more detail later.

Still more recently, a series of reports has appeared in the literature describing experiences with burning feet among allied prisoners of war in widely scattered Japanese prison camps. In general, these reports indicate an extremely high incidence of burning feet in the deficiency states encountered in the prisoners of war. Katz²² reported his experiences with the condition in American prisoners of war at Cabanatuan in the Philippines and estimated that 2,000 instances of what the men called "hot foot and hand disease" were observed from January to June, 1943. Gottlieb²³ described the condition in patients at the Shinagawa Prisoner of War

Hospital in Tokyo. Smith²⁴ mentioned 700 instances of "electric feet" or "burning feet" which appeared in Hong Kong in a civilian internment camp with a population of 2,500. Harrison²⁵ claimed that "the outstanding symptom of nutritional deficiency in prisoners-of-war in Hong Kong was painful feet." Simpson²⁶ and independently Dunlop²⁷ described burning feet in prisoner of war camps in Java. Simpson reported an incidence of 200 to 300 patients in the average camp of 1,500 to 2,000 men, while Dunlop estimated involvement of as many as one third of the prisoners of war. Cruikshank²⁸ reported a study of 500 patients at the "Changi" camp in Singapore. Coates²⁹ described the syndrome in prisoners of war in Burma while Stenning³⁰ claimed that eighty-five of 300 men, an incidence of 28 per cent, were affected in a camp in Japan.

CLINICAL PICTURE AND EXPERIENCES WITH BURNING FEET

The following account deals with the author's experiences with burning feet among prisoners of war in the Philippines and Japan. The Philippine observations relate to the Bilibid Prisoner of War Hospital in Manila and Cabanatuan, the central camp for prisoners of war on Luzon. The Japanese experiences relate to the Stadium Hospital in Osaka and the Kobe Prisoner of War Hospital.

Burning Feet in the Philippines. Although the war in the Far East began in December, 1941, and evidence of weight loss and malnutrition soon became apparent among the American troops in the Philippines, it was not until July or August, 1942, three or four months after the surrender of the Americans, that the first patients with burning feet began to appear. The incidence of this condition rapidly increased until in November and December, 1942, it constituted a major epidemic. Toward the end of 1942,

at the Bilibid Prisoner of War Hospital in Manila approximately 300 of some 800 patients hospitalized for various causes complained of burning feet. Since Bilibid drew its patients from camps scattered throughout Luzon the incidence of this condition at Bilibid reflected the widespread appearance of the syndrome in the Luzon camps. The occurrence of some 2,000 such cases at Cabanatuan from January to June, 1943, has already been mentioned. There were numerous evidences of malnutrition and avitaminosis among the prisoners of war at this time. Various degrees of weight loss and ankle edema were seen. Typical pellagra rashes were extremely common. Fissuring at the corners of the mouth, glossitis, scrotal dermatitis, night blindness, corneal ulcerations, amblyopia with constriction of visual fields and central scotomata were all very common. Diarrhea, whether on a pellagrous, parasitic or bacillary basis, was practically universal. Burning feet frequently occurred in conjunction with one of these manifestations or developed in patients who either had or later developed evidences of these deficiencies. However, the striking thing appeared to be that it could occur as a distinct symptom complex by itself.

The onset of this condition was gradual with subjective complaints of numbness, pins-and-needles or tingling in the toes and feet. As a rule these occurred bilaterally. After a week or two the paresthesias gradually gave way to burning pains in the toes and soles of the feet. In more severe cases, after a variable period of days or weeks, patients began to complain of typical, sharp, periodic shooting pains. These pains did not replace the burning sensation but occurred as an added phenomenon in severe cases. The shooting pains generally radiated from the dorsa of the feet between the first and second toes up the legs in a severe, shock-like fashion. An interesting

and striking phenomenon was the definite relationship of both the burning and lancinating pains to the time of day. Patients practically always complained that pains were worse at night than during the day. Beginning in the late afternoon the pains would gradually increase in severity until at bedtime sleep would be impossible. After reaching maximum intensity late at night or early in the morning, the pains would gradually subside, although rarely disappear, until the beginning of the next torturing cycle.

In severe cases the patients also occasionally complained of pains in the palms of the hands. This, too, was bilateral. Pains in the hands were not nearly as frequent as foot pains and when present, in the author's experience, they were never as severe as foot pains. Furthermore, the author never saw a patient who had only his hands involved.

In some patients, during severe paroxysms of the pain, sweating of the affected parts was noted. The sweating involved the parts in which the patient complained of the most severe pains. It was quite definite and striking and appeared fairly well delineated. The foot, particularly its distal portion, was involved. During the paroxysms of pain and sweating the involved areas felt somewhat cooler than normal to the touch. However, except for occasional slight pallor, they showed no color changes. In the author's experience the affected parts did not become red or cyanotic. This is in agreement with the experience of many observers although others claim to have found varying degrees of redness and cyanosis of the feet and hands.

Quite as striking as the cyclical character of the pain was the relief of pain with cold water. Patients practically always discovered for themselves that some degree of relief could be obtained by soaking their feet in cold water. This they frequently did several times a day. A cold shower at bedtime was another method of obtaining some relief.

Although these measures did not abolish the pain completely, they did make the condition more bearable. Conversely, heat and warm water seemed to aggravate the pain.

Plantar hyperesthesia and hyperalgesia were universal phenomena in all but the earliest and mildest cases. In moderately severe cases touching or scratching the sole of the foot caused unbearable pain. Strangely enough, when slight pressure was slowly and gently applied to the sole of the foot the patient did not complain of pain. Indeed, one of the common methods of obtaining some relief was the simple procedure that the patients adopted of clasping the distal portions of their feet in their hands and applying cautious and gentle pressure. In contrast to this was the sharp withdrawal and agonized cry of pain when the examiner attempted to elicit the Babinski sign. Fortunately, bed clothes were no problem since in the warm weather of the Philippines these were not necessary.

The condition as just described was a chronic one; nevertheless, on examination the deep tendon jerks were preserved. Occasionally, knee jerks and somewhat more frequently ankle jerks appeared diminished but preservation of reflexes was the rule. With exceptions which will be given later, spinal cord involvement did not occur. At Bilibid evidence of pyramidal tract disease was not seen. Hoffman, Babinski and confirmatory signs were negative. Knee and ankle clonus could not be elicited. There was no spasticity. Motor power was preserved. There was no paralysis of the lower extremities. The patients showed no evidence of foot drop. Even in the most severe cases, when the patients were sufficiently coaxed to disregard the pain involved in these tests they could be induced to stand on their toes or their heels.

The gait was peculiar but this appeared to be due to pain and hypersensitivity of the soles of the feet rather than to disturbance

of motor power or equilibrium. The patient walked as if the ground beneath the soles of his feet were hot. He walked cautiously, gingerly, and on a somewhat widened base. Because of his reluctance to use his oversensitive toes to grip the ground, the gait had a characteristic flat-footed quality. In standing, patients frequently shifted their weight from one foot to the other in a restless and repetitious fashion. It seemed as if they could not endure the discomfort of resting their weight on one foot for more than a few moments at a time. The same restlessness was frequently noted while the patient was in bed. Often when the pain was severe patients would sit cross legged in bed, holding the distal portions of their feet in their hands and rock rhythmically backward and forward with the pain. This last attitude was not only pitiful but it was so pathognomonic that any observer walking into a ward could pick out those with burning feet at a glance.

Careful sensory examination generally revealed some degree of objective sensory involvement in marked conditions. The involvement was bilateral. Proximal to the zone of hyperalgesia and hyperesthesia, sensory diminution could be demonstrated for variable distances up the legs and even as high as the mid-thigh. Diminished sensibility was more severe distally and gradually decreased to an indefinite border proximally. Diminution of sensation rather than complete loss was the rule. The author did not see complete or clearcut anesthesia. All forms of sensation were involved. The involvement was uniform, not patchy. Occasionally the involvement assumed the sock or stocking type of distribution, at other times the upper limit of involvement, which was difficult to map accurately because it was never clearcut, was irregular in outline, not conforming accurately to either segmental or peripheral nerve patterns. As for the various sensory modalities, decrease of

pain and touch proximal to the hyperalgesia and hyperesthesia could usually be readily demonstrated. Sense of position, if at all involved, was only mildly diminished and then only in the toes. Diminished vibratory sensibility not infrequently could be demonstrated in the ankles and toes. Impairment of appreciation of hot and cold could usually be determined somewhat more easily than impairment of the other forms of sensation.

Despite the fact that this condition frequently persisted for years trophic changes were not remarkable. Katz,²² who described burning feet in American prisoners of war at Cabanatuan, noted atrophic, thin, tightly stretched skin in the hands and feet of some patients. Trophic changes of this order have not been reported by other observers and the author from his own experience cannot confirm Katz's observations.

The condition of the musculature appeared to depend on the general nutritional state of the patient. With evidence of marked weight loss there was generalized wasting of muscle, otherwise loss of muscle was not striking. An exception to this was a moderate degree of atrophy in the intrinsic muscles of the feet which was often demonstrable in those patients with moderately severe involvement. It is possible that this was due to atrophy of disuse resulting from the disinclination to use the toes in walking. The dorsalis pedis and posterior tibial arteries in these patients were always patent and readily palpable.

Results with Therapy. Attempts at therapy were disappointing. Nicotinic acid, 100 mg. by mouth per day for ten days, dramatically relieved associated signs of pellagra but was without effect on the symptoms of burning feet. Thiamin chloride was available only at irregular intervals but the impression gained from its use was that parenteral doses up to 50 mgm. per day were not particularly effective. Controlled studies on other members of the vitamin B

complex could not be undertaken because these vitamins were not available in adequate amounts. Quinine sulfate in doses of 1 to 1.3 Gm. per day by mouth seemed to ease the pain slightly in some patients. Analgesics were only mildly effective and as a rule the only real relief obtained was with narcotics. In two patients procaine infiltration of the posterior tibial nerve at the medial malleolus was attempted. This procedure relieved the pain. Coates²⁹ has reported relief in one patient by the more drastic procedure of section of the tibial and superficial peroneal nerves.

This description is essentially the picture of the condition as the author saw it in the Philippines among American prisoners of war. It is possible that this represented only the initial stage of a more extensive neurologic syndrome which for complete evolution requires poorer dietary conditions than those that were present in the Philippines. In support of this possibility is information the author has received that one of his patients with burning feet eventually developed signs of spinal cord involvement.³⁰ Urinary sphincter disturbance and signs of pyramidal tract and posterior column involvement appeared. Similarly, Cruikshank²⁸ at Singapore noted the development of spastic paraplegia and quadriplegia with definite signs of upper motor neuron involvement in a few of his patients with painful feet.

Burning Feet in the Hong Kong, Singapore and Java Camps; and the Diet. It is rather remarkable that burning feet appeared almost simultaneously in such widely separated areas as Hong Kong, Singapore, Java and the Philippines. Smith²⁴ dated the onset for a Hong Kong camp as July, 1942, Cruikshank²⁸ noted it the end of July, 1942, in Changi in Singapore, and Simpson²⁶ recognized the appearance of the condition in July, 1942, in the Java camps. The onset at Bilibid has already been noted. Following

the onset at Bilibid the number of new patients rapidly increased through the fall of 1942, reached a maximum in the winter of 1942, and then declined after the arrival of Red Cross food parcels* and some bulk food at the end of December, 1942. The decline appeared to be maintained by generally improved food conditions through the first half of 1943. Cruikshank²⁸ noted a similar rise at Changi in Singapore with an abrupt drop in the number of new patients following the arrival of Red Cross supplies and generally improved dietary conditions in November, 1942.

The diets which have been reported from these areas are very similar. For the Java camps Simpson²⁶ listed the diet as "polished rice—400 g., vegetables 200–250 g., meat—50 g., bread 50 g., coconut oil—10 g., salt—5 g." Smith²⁴ indicated a similar diet for his Hong Kong camp but did not give the quantities of the individual constituents. At Bilibid the diet from which burning feet developed was essentially the same as the Java camp diet. The total quantity of rice and the degree of milling varied from time to time. The meat was replaced by fish or omitted periodically and the vegetables were usually leafy greens. At Bilibid the vegetables were invariably boiled and the rice was cooked either dry or as gruel.

Paucity of New Patients and the Diet in Japan. In Japan while at the Kobe Prisoner of War Hospital† the author did

* A sample parcel from the American Red Cross contained the following items: 14½ oz. tin evaporated, irradiated milk; 8 oz. pkg. biscuits; 8 oz. pkg. Borden's American cheese; 8 oz. tin instant cocoa; 15 oz. tin sardines; 1 lb. tin oleomargarine with vitamin A; 12 oz. tin corned beef; 12 oz. tin sweet chocolate; 2 oz. pkg. granulated sugar; 7 oz. tin powdered orange concentrate (vitamin C); 5 oz. pkg. dehydrated soup; 16 oz. pkg. prunes; 4 oz. tin instant coffee. Each individual received the equivalent of two and one-half parcels.

† The Kobe Prisoner of War Hospital drew patients from the camps in the Osaka command. This included some twenty camps scattered from the east to the west coast of central Honshu, with a total population of approximately 10,000 prisoners of war. The nationalities represented in these camps were British, American, Australian, Dutch, Javanese, Eurasian and Canadian.

not see any new patients with burning feet. There was a report of several supposedly new cases which developed in the Netherlands East Indies troops in a camp in the Osaka command and the author did see a few instances of recurrence in patients who first developed the condition in the southern areas (the Philippines, Hong Kong, Singapore, etc.). However, the paucity of new patients and the low rate of relapse of old patients in the Osaka area was rather surprising. In this region of Japan the diet differed from that noted for the Java and southern camps in one significant respect. The major portion of the southern diet consisted of only one grain and this was rice, whereas in the Osaka camps varying proportions of barley, millet seed and soya beans were always issued with the rice. It is possible that these constituents to some extent protected against the development of burning feet by supplying a factor which was deficient in the single grain (rice) diets. Gottlieb²³ and Stenning³⁰ reported burning feet in prisoners of war in Japan, but it is difficult to evaluate their experiences in this matter since these authors did not specify whether they were dealing with patients who developed the condition in Japan or patients who had developed the syndrome in the southern regions and were still suffering with the condition on arrival in Japan.

Development of Gangrene in Japan. A second observation of interest in the Osaka command camps, and this has been noted by Gottlieb²³ and Stenning³⁰ in other areas of Japan, was the occurrence of several cases of what the Japanese called "spontaneous gangrene." This developed in the toes and distal portions of the feet in a small number of patients with burning feet and required amputation of the distal portion of the involved extremity. In connection with the patients that developed gangrene it is important again to mention the pernicious habit which the patients with burning feet

practiced, that of obtaining relief by means of chilling the feet. In Japan they frequently walked the brick floors of the huts or barracks barefooted at night, despite the fact that the camps were practically unheated and the winters were so severe that several inches of snow were present in the camps on the east coast and several feet of snow in those on the west coast of Central Honshu. Frostbite may very well have been a factor in the production of this gangrene, these patients perhaps being more susceptible to frostbite than others. The amputations were always low, just above the gangrenous region, the wounds healed slowly but the stumps remained healthy and re-amputation was not required.

Unfortunately, it was impossible to carry out pathologic studies on the surgical sections or on patients who died of intercurrent disease. In February, 1945, however, Dr. R. Kinoshita, Professor of Pathology at the Osaka Imperial University, supplied some information on the pathologic features of this condition. Kinoshita³² claimed that the Japanese had been unfamiliar with the syndrome of burning feet before the war. However, they began to see patients with this condition among the Japanese military personnel who had been cut off by allied operations in the southern battle areas for variable periods of time before rescue. These patients while in the "by-passed" regions had subsisted on reduced rations but details of their diet for purposes of comparison with that of the prisoners of war were unobtainable. Kinoshita claimed to have autopsied a small number of these Japanese patients with burning feet who died of intercurrent conditions such as tuberculosis, etc., and he observed that the spinal cords and peripheral nerves in these patients were normal. He did find changes in the small arteries, whose walls were diffusely thickened, and he commented on the absence of new vessels. Kinoshita also noted that gangrene did not

develop among Japanese with burning feet while these patients were in the southern areas. Several patients did develop gangrene after their return to Japan.

COMMENT

For well over a century since Grierson's¹ description of the syndrome in 1826, burning feet received only sporadic attention in journals of tropical disease. For those who have not had any direct experience with the condition it has remained an obscure tropical affliction consigned to a few lines of small print in tropical disease texts. Peraita's²⁰ observations during the Spanish Civil War, however, and the recent reports dealing with Japanese prisoners of war indicate that when proper circumstances of malnutrition prevail this syndrome may appear in very high incidence and affect large segments of the population. Certainly in the regions mentioned burning feet exceeded classical dry beriberi as a deficiency manifestation, both in frequency of occurrence and in anguish caused the patient. From the standpoint of potential numerical significance alone, burning feet is deserving of further study. Other aspects of this disorder make the entire problem one of great interest.

Relationship to Vitamin Deficiency. A review of the existing literature on burning feet has revealed remarkably consistent descriptions of this condition by different authors. The association with malnutrition and a poor diet has been invariable and a close relationship with B complex deficiency, such as ariboflavinosis and pellagra, has been mentioned repeatedly.

The author has mentioned the frequent occurrence of other evidences of malnutrition in association with burning feet at Bilibid and this point should be stressed. Patients who developed burning feet at one time or another often presented pellagra rashes, scrotal dermatitis, glossitis, fissuring at the corners of the mouth, corneal ulcera-

tions, visual diminution with central and paracentral scotomata, ankle edema and diarrhea. The syndrome of burning feet has been described by itself because none of these associated signs seemed to be essential concomitants. Frequently these associated signs disappeared with treatment or some dietary variation which did not influence the course of the pain. Landor and Pallister³¹ described a deficiency syndrome in Malayan prisons which they called avitaminosis B₂ since the manifestations responded to treatment with autoclaved yeast or marmite. In this syndrome they included scrotal eczema, superficial glossitis, eczema of the angles of the mouth, foot pains, poor vision (due to retrobulbar neuritis) and combined degeneration of the cord. Stannus,³³ although he admitted the possible rôle of other deficiencies, suggested that this syndrome including the foot pains was due to hyporiboflavinosis. There is no proof that the entire Landor and Pallister syndrome is due to riboflavin deficiency or, in fact, that it is due to any single deficiency. The response to autoclaved yeast simply indicates response to the heat-stable factors in the vitamin B complex. Riboflavin is merely one of these factors. The Landor and Pallister syndrome could well be the result of a multiple deficiency from the lack of several factors in the B complex. This is borne out by Gopalan's work which indicates that burning feet may actually be due to pantothenic acid deficiency. Gopalan²¹ noted the frequent occurrence of glossitis, angular stomatitis, angular blepharitis, superficial keratitis and scrotal dermatitis in his patients with burning feet. He claimed that with riboflavin the associated signs rapidly disappeared, whereas the burning pains were unaffected. Gopalan obtained complete relief of the burning pains with vegemite, no relief with thiamin chloride or nicotinic acid, and rapid relief with calcium pantothenate. The relief with calcium pantothenate was even more impressive

than the improvement with vegemite. Although Gopalan's therapeutic results with calcium pantothenate were striking, confirmation of his work and further studies on the relationship of pantothenic acid to burning feet will be necessary before a final estimate of the significance of pantothenic acid in this condition can be made.

If a relationship between pantothenic acid and burning feet can be established, this will be of some importance since the significance of pantothenic acid in human nutrition has not as yet been clarified.³⁴ Pantothenic acid has been known as the filtrate factor or chick antidermatitis factor.³⁵ It is at least one of the achromotrichia factors in the rat. Extensive neuropathologic changes due to deficiency of this factor have been demonstrated in chicks,³⁶ mice³⁷ and pigs.³⁸ It may be of interest at this point to call attention to some unusual symptoms that have been noted in pantothenic acid-deficient mice and pigs, although no attempt will be made to draw conclusions from these incidental findings.

Wooley³⁹ noted that after three weeks on a pantothenic acid-deficient diet his mice became hyperirritable and a few days later they "seemed to be seized by periodic spasms of pain, for at intervals very violent and rapid movement would take place and the animals would squeal occasionally, as if in pain." This behavior lasted a few days and then the violent movements subsided and paralysis of the hind legs developed. In speaking of pantothenic acid deficiency in the pig, Follis and Wintrobe⁴⁰ stated that "one of the first signs of neurological involvement is a sudden lifting of one of the limbs from the ground as though it were painful."

Pain in Burning Feet. There are some striking similarities between burning feet and the state which Thomas Lewis^{41,42} calls erythralgia. In both conditions such phenomena as localized hyperalgesia and

burning pains which are relieved by cold and increased by heat occur. The pain in burning feet bears marked resemblances to the pain in erythromelalgia¹³ and Lewis classes erythromelalgia with conditions that manifest erythralgia. Because of these similarities, it seems reasonable to suspect that the mechanisms which determine the pain in burning feet are similar to those which determine the pain in erythralgia.

In erythralgia⁴² there is a generalized lowering of the pain threshold for all forms of stimuli, presumably due to a state of overirritability of the nerve endings transmitting impulses of pain. As a result of these lowered thresholds, which are manifested as localized hyperalgesia, heat elicits burning pain at considerably lower temperatures than are required in normal skin. In normal skin pain is evoked by water at a temperature of 43°C., whereas in experimentally induced erythralgia⁴² and in erythromelalgia⁴³ temperatures of approximately 32° to 34°C. and 33° or 34°C., respectively, suffice. Since the latter temperatures are so near the ordinary range of skin temperatures such factors as the warmth of a room, the presence of bed clothes or even local vasodilatation can elevate the temperature of erythralgic skin above these lowered thresholds and thereby produce pain. Conversely, when the skin temperature falls below these thresholds, as with the action of cold water, the pain is relieved. The ease with which similar mechanisms would explain the influence of temperature on the pain in burning feet is apparent.

Furthermore, it is known that the body temperature of a given individual shows diurnal fluctuations of 0.5°F. to 1.0°F. The maximum temperature occurs in the late afternoon or early evening and the minimum occurs at approximately 4 or 5 in the morning.⁴⁴ The possible relation of this phenomenon to low pain thresholds for heat and the pain cycle in burning feet provides a

point of interesting speculation. The pain in burning feet characteristically begins in the late afternoon or early evening and improves in the early morning.

Lowered pain thresholds for tissue stretch explain the influence of intravascular hydrostatic pressure on the pain in erythralgia.⁴² Lewis has demonstrated that obstructing the venous return from erythralgic skin induces pain. Pain is relieved, however, if pressure is applied directly to the erythralgic skin in amounts which counterbalance the venous pressure in the cutaneous veins. Here again, an analogous situation in burning feet would explain the relief some patients obtained from gentle pressure in the foot-holding attitude described previously.

Proof of the applicability of the above mechanisms to burning feet awaits the actual determination of lowered pain thresholds in this condition. Such a demonstration would be significant from another standpoint, in that it would indicate a peripheral and local mechanism for the pain and hyperalgesia in burning feet rather than a central mechanism. Hardy, Wolf and Goodell⁴⁵ have measured the pain threshold for heat in the hyperalgesias associated with such conditions as referred pain, syringomyelia, lesions near the thalamus and in root and nerve disease. They found that, excluding hysteria and malingering, only inflammation of the skin or damage to tissue near the peripheral nerve endings for pain produced lowered pain thresholds.

Vascular Involvement. The development of gangrene in some patients in Japan points to vascular involvement in burning feet. Kinoshita's claims³² in regard to his pathologic observations are in accordance with this explanation. Sweating was observed during the paroxysms of pain in some patients and with this the feet felt somewhat cooler to the touch. However, what part the sympathetic nervous system and vasospasm played in the entire picture is difficult to

say. Skin temperatures were not accurately measured and with the exception of the instances mentioned during the paroxysms of pain, no difference could be detected by touch between the temperature of the feet in patients with burning feet and the temperature of the feet in normal individuals.

Correlation and Interpretation. Because of the lack of accurate information concerning the pathologic condition of burning feet any attempt to correlate and interpret the major phenomena in this condition must be largely speculative. Nevertheless, the underlying disorder is a nutritional one and the possibility that it may be a specific pantothenic acid deficiency must be considered. This disorder damages various susceptible tissues probably by interfering with the metabolism of these tissues. Damage to peripheral tissue in the neighborhood of the nerve endings responsible for pain, with irritation of these endings, and the production of a state similar to the erythralgic state would explain the pain in burning feet. Damage to the small arteries of the feet, as seen by Kinosita, probably reduces the circulatory efficiency of the feet and renders them susceptible to gangrene which results from repeated exposure to cold. The sensory diminution in the lower extremities indicates mild involvement of the nerves to these extremities. This involvement could be due to ischemia secondary to the circulatory impairment or it could be due to a neuropathy caused by the basic nutritional disturbance. The fact that the basic disturbance may damage nervous tissue is indicated by the development of signs of spinal cord disease in a few patients.

Burning Pains in Pellagra. The frequency with which evidence of pellagra occurred in the patients with burning feet in the Philippines has been mentioned. When patients presented both these conditions, nicotinic acid alone, without alteration of the diet, dramatically relieved the pellagra manifestations without improving the symp-

toms of burning feet. Burning of the soles of the feet has been described as one of the most common neurologic symptoms of pellagra.⁴⁶ Without denying that pellagra alone may produce burning foot pain, the possibility should be considered that burning pains associated with pellagra may indicate the presence of more than one deficiency state. The possible concomitant occurrence of burning feet with pellagra should be borne in mind.

Synonyms for Burning Feet. From time to time various names have been employed to denote the syndrome discussed in this paper. Generally, these have been unsatisfactory. In "Manson's Tropical Diseases"⁴⁷ a brief and confusing paragraph has been devoted to burning feet and the terms "chachaleh" and "barasheh" have been employed as synonyms. In the author's opinion these synonyms are not justified. Buchanan⁴⁸ described one hundred cases of what appears to be a mixed deficiency syndrome in natives of British Somaliland and he employed the terms "chachaleh" or "barasheh" to denote this syndrome. Burning feet was only an associated manifestation in this symptom complex since only 39 per cent of the patients had this complaint, whereas 82 per cent had edema, 41 per cent brawny edema, 60 per cent generalized aches, 53 per cent joint pains and 45 per cent complained of pains in the back of the neck and shoulders.

The name that has been most frequently used to date has been the term "burning feet." For obvious reasons this name is an unsatisfactory one. Since burning of the feet is one of the most common complaints referred to the lower extremities, the phrase burning feet may indicate a host of conditions. It fails to designate a specific syndrome. Collas⁵ suggested the name *causalgésie* or *causalgia* and later Peraita used the phrase *paresthetic-causalgic syndrome* for what was essentially burning feet

in Madrid. The objections to these terms are that they fail to indicate the nutritional factor in the syndrome and that the word causalgia through usage implies features which are not part of burning feet. Causalgia, as derived from the Greek by S. Weir Mitchell, means burning pain. Mitchell coined this word to designate the burning pain associated with nerve injuries. With usage, however, the word has come to imply not only burning pain but a complete syndrome which follows nerve injury. Burning pain is the most prominent aspect of this syndrome but trophic skin changes such as glossy skin and a local rise in temperature are included in this picture.⁴⁹

The condition that has been called burning feet is deserving of a better name. In the absence of such a name the author wishes to suggest the term "nutritional melalgia." The word melalgia is derived from the Greek and means limb pain. The name nutritional melalgia, therefore, indicates nutritional limb pain and expresses the major characteristics of the syndrome that has been discussed in this paper.

SUMMARY

1. The historical development of the syndrome called burning feet has been outlined.

2. The clinical features of this condition as it was seen in the Philippines and Japan have been described and experiences with this condition have been recorded.

3. The nutritional basis of the syndrome and the character of the pain have been discussed.

4. The name nutritional melalgia has been suggested to replace the original designation of burning feet.

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Seminar on Thromboembolism

Postoperative Thromboembolism^{*}

Some Remarks on the Influence of Early Ambulation

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EARLY rising from bed and walking preclude the protracted period of inertia which traditionally follows in the wake of surgery and permit the prompt resumption of normal activity. Many postoperative complications are favorably effected by such a program. Unfortunately, the incidence of thrombosis, of suspected thrombosis, and of thrombosis and embolism together is unaltered. Fatalities from massive pulmonary embolism, however, are less common than they were before the revival of early postoperative ambulation.

In support of these statements the following clinical study of 1,519 major surgical cases is presented. All of the patients have been under the author's personal supervision or observation and, in addition, all the tables have recently been meticulously reviewed by him or by Dr. Brantley Holt to whom he is indebted for much assistance with the collection of these data.

PRELIMINARY REMARKS

In any such investigation it is imperative that the clinical charts be complete, that the data be accurately recorded and that the diagnoses be correctly tabulated and filed. Even under the most ideal circumstances, in which the patient's record is finally reviewed and the diagnoses appended at staff meeting before tabulation and filing in a record room where secretarial

and clerical assistants are trained and conscientious, secondary diagnoses are occasionally not included. Hence, they are lost to any clinical study which is based only upon a perusal of the front unit sheets or punch cards. For that reason the author believes that many reports on the incidence of postoperative thrombosis and embolism, both before and after the reintroduction of early postoperative activity, may not represent the actual frequency of these complications.

Several obvious thrombotic and embolic phenomena were discovered in this review which were not recorded among the diagnoses nor tabulated in the files. Except for the critical examination of each record, these cases would not have been included and the results and conclusions would have been correspondingly invalidated by their absence.

The pattern of surgical convalescence is undergoing such fundamental reforms so rapidly that much confusion exists in the literature on the connotation of "early postoperative activity" or "ambulation." It seems desirable, therefore, to establish a uniform terminology and it is herewith suggested that the word "immediate" be applied to postoperative ambulation which begins promptly after termination of the operation and anesthesia, walking from the table to bed as some authors advocate; that "early" be reserved for those patients who

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get out of bed and walk not immediately after operation but within the first twenty-four hours; that "accelerated" be used for activity which begins on the second, third, or fourth days; and that "traditional" or "delayed" be employed when referring to postoperative walking which is not undertaken until the fifth day or after.

Such a classification will be followed from henceforth in this discussion. The term, thrombosis, will be used to signify both the bland type and thrombophlebitis.

PRESENTATION OF CLINICAL DATA

The data herein presented have been compiled from the records of 1,519 surgical patients who had been operated on at the Mary Imogene Bassett Hospital by the two senior attending surgeons, by the resident surgeons, and rarely by the interns with senior assistance. The cases are unselected and overspread a period of a little more than five years prior to October, 1946.

Six categories of major operations have been included: (1) hernioplasties of all types, (2) appendectomy for acute appendicitis of all grades of severity with and without drainage, (3) cholecystectomy for acute and chronic cholecystitis and cholelithiasis with and without exploration and drainage of the common duct, (4) abdominopelvic surgery for all major gynecologic abnormalities, (5) all operations on the genitourinary tract and (6) a miscellaneous group of abdominal cases, gastrointestinal, colonic and abdominoperineal resections, thoracic procedures, radical mastectomies, thyroidectomies and operations on extremities with internal fixation of both recent and old fractures.

The patients in each of these major operative groups separate themselves on a temporal basis of postoperative activity into subgroups representing early, accelerated and delayed ambulation. (Table I.) "Early" connotes rising from bed and walking within

a period of six to twenty-four hours after operation; "accelerated" indicates ambulation on the second, third or fourth day. "Traditional" implies delayed activity; these patients spent an average of 12.1 days in bed. The author has had no experience with "immediate" postoperative ambulation.

In each major operative group there were one or two deaths not from embolism, seven among the urologic patients within a few hours to a few days after emergency operations for acute lesions or radical procedures for advanced disease in elderly patients. These are included in the total mortality but have not been considered when compiling the incidence of thrombosis and embolism, or the mortality from pulmonary embolism, coincidental with early, accelerated or delayed convalescence. There were also 116 children under thirteen years of age in the total series who likewise are not included in the statistics on thromboembolism. (Table II.)

All the data are presented in tabular form in Table II which requires very little additional explanation. In some cases the clinical diagnoses of thrombosis and embolism were obvious, in a few they were proved by postmortem examination and in still others they could only be suspected. Suspicion, however, was in all cases well founded. In thrombosis of the deep veins of the legs it was based always upon two, at least, of the signs characteristic of this complication, namely, pain, discomfort, soreness, or tenderness in the calves of the legs, thickening or induration of the muscles of the calves, edema or swelling of the legs or ankles, increased prominence of the superficial veins, elevation of the cutaneous temperature and a positive dorsiflexion sign (Homans' sign), usually accompanied by a low grade fever and very often by an elevation of pulse rate above the curve representing the temperature. In a few instances

the evidence was transitory in character but was of sufficient significance, in the opinion of the author, to justify the diagnosis of probable or suspected thrombosis. Hence it is believed that these patients with even minimal signs should be included in this

Unlike Blodgett and Beattie² the author does not include thrombosis even as a probable diagnosis in cases of embolism in which no thrombosis is manifest. Its existence is presupposed when embolism occurs in patients with no cardiac disease but the

TABLE I
TABULATION OF ALL THE CASES UPON WHICH THIS STUDY IS BASED

Postoperative Activity	Operations						Total
	Hernioplasties	Appendicectomies	Operations on Biliary Tract	Abdominopelvic Cases	Operations on Genitourinary Tract	Miscellaneous Cases	
Early ambulation (ambulatory within 6-24 hours after operation) . . .	116	68	65	70	116	102	537
Accelerated activity (ambulatory 2nd, 3rd or 4th day)	14	11	25	26	91	37	204
Traditional convalescence (average of 12.1 days in bed)	75	109	92	200	89	82	647
Died—not up (within a few hours to a few days after operation)	2	2	1	1	7	2	15
Children under 13 years of age	42	42	0	0	6	26	116
Total	249	232	183	297	309	249	1519

study of the incidence of thromboembolism for it is now well established that clinically unrecognizable bland thrombosis of the deep veins of the legs occurs many times among elderly surgical and medical patients who are confined to bed.¹

The occurrence of probable or suspected embolism was supported in all cases by sudden pain in the chest, aggravated by breathing, usually followed by fever for three to four days, and often by a little fluid in the pleural cavity. When these signs were accompanied by hemoptysis, with or without the demonstration of a wedge-shaped shadow in the periphery of the pulmonary field by roentgenographic examination, a definite diagnosis of pulmonary embolism was made, even though the source of the thrombus was not apparent.

There were eleven patients in the first category and one in the second.

diagnosis should not be made unless it can be supported by clinical symptoms and signs.

Among the patients who were ambulatory within twenty-four hours after operation and discharged from the hospital a few days later there were four who developed thrombosis and one who had both thrombosis and embolism at home. Had these patients returned to the care of family physicians in distant communities these cases might well not have been reported and hence lost to any statistical study on the incidence of postoperative thromboembolism. Early discharge from the hospital is common in clinics where patients are ambulatory on the first postoperative day and the above situation often repeated and not reported to the operating surgeon or to the hospital may account in part for the low incidence of thromboembolic complications recorded by

some authors after early postoperative activity.

In the series herein discussed the incidence of thromboembolism among the patients who were out of bed and walking within twenty-four hours after operation

bolism was 5.4 per cent, very comparable to that in the two series in which earlier activation was permitted; the mortality from fatal embolism, however, was twice as great, namely, 1.08 per cent, as compared with 0.49 per cent and 0.56 per cent.

TABLE II

DETAILED TABULATION OF THE DATA FROM WHICH HAVE BEEN COMPUTED THE INCIDENCE OF THROMBOSIS AND EMBOLISM AND THE MORTALITY FROM EMBOLISM IN RELATION TO POSTOPERATIVE ACTIVITY; APPENDED ALSO ARE ADDITIONAL STATISTICS ON TOTAL MORTALITY FOR THE ENTIRE SERIES OF 1,519 CASES

Activity	Operative Grouping	Thrombosis	Embolism	Thrombosis and Embolism	Suspected Thrombosis	Suspected Embolism	Suspected Thrombosis and Embolism	Total Cases of Thromboembolism	Deaths from Other Causes	All Cases Analyzed	Incidence of Thromboembolism, %	Deaths from Embolism	Mortality from Embolism, %	Early Deaths not Previously Included	Children under 13 Years	Total Cases	Total Deaths	Total Mortality, %
Early Ambulation	Hernioplasty . . .	2		1	1	2		6	0	116	5.2	0	0					
	Appendicectomy .	1						1	0	68	1.4	0	0					
	Biliary surgery . .				1	1		2	3	65	3.1	0	0					
	Abdominopelvic .	2			3		1	6	0	70	8.5	0	0					
	Urologic surgery .	2		5				7	0	116	6.0	2	1.7					
	Miscellaneous . . .	4	1				4	9	0	102	8.8	1	0.9					
	Total	11	1	6	5	3	5	31	3	537	5.8	3	0.56					
Accelerated Ambulation	Hernioplasty . . .							0	1	14	0	0	0					
	Appendicectomy .							0	0	11	0	0	0					
	Biliary surgery . .	1			1			2	1	25	8.0	0	0					
	Abdominopelvic .	2						2	0	26	7.7	0	0					
	Urologic surgery .	2				2	1	8	2	91	8.8	1	1.1					
	Miscellaneous . . .			1		1		2	0	37	5.4	0	0					
	Total	5	0	4	1	3	1	14	4	204	6.8	1	0.49					
Delayed Ambulation	Hernioplasty . . .	1		2		1	1	5	2	75	6.6	1	1.3					
	Appendicectomy .	1		1	1	1		4	0	109	3.7	1	0.9					
	Biliary surgery . .	2			2	1		6	3	92	6.5	1	1.1					
	Abdominopelvic .	4		2	1	2	1	10	0	200	5.5	2	1.0					
	Urologic surgery .			1	1		2	4	3	89	4.5	1	1.1					
	Miscellaneous . . .	4		1			1	6	2	82	7.3	1	1.2					
	Total	12	0	7	5	5	6	35	10	647	5.4	7	1.08					
All Cases	Total	28	1	17	11	11	12	80	17	1388	5.8	11	0.79	15	116	1519	43	2.8

was 5.8 per cent and the mortality from fatal embolism was 0.56 per cent; among the patients who were ambulatory on the second, third or fourth days the incidence was 6.8 per cent and the mortality 0.49 per cent. In the control group of 642 patients who remained in bed for an average period of 12.1 days the incidence of thromboem-

(Table II.) These figures alone permit the deduction that early or accelerated postoperative activity does not alter the incidence of thromboembolism but does reduce the number of deaths from thrombi of sufficient size to precipitate fatal postoperative catastrophies.

The analysis, however, fails to indicate

and take into consideration one very important therapeutic agent which was introduced more or less concomitantly with early postoperative activity, namely, section and ligation of the femoral vein when the diagnosis of thrombosis in the deep veins of

TABLE III

TABULATION OF MORTALITY OF THROMBOEMBOLISM FOLLOWING NON-OPERATIVE CONSERVATIVE THERAPY AND AFTER SECTION AND LIGATION OF ONE OR BOTH FEMORAL VEINS—FLOATING AND ADHERENT THROMBI WERE FREQUENTLY ASPIRATED BY SUCTION BEFORE LIGATION OF THE VEIN

Cases	Activity			Total
	Early	Accelerated	Delayed	
Patients with thromboembolism.....	31	14	35	80
Not operated upon....	26	12	32	70
Deaths.....	3	1	7	11
Mortality.....	11.5%	8.3%	21.9%	15.7%
Treated by operation..	5	2	3	10
Deaths.....	0	0	0	0
Mortality.....	0	0	0	0

the legs is apparent. At first the operation was limited to one side if only one leg were clinically involved. With acquisition of the realization that thrombosis in the deep veins of the lower extremities is almost always bilateral, both veins have subsequently been divided and ligated, even though symptoms and signs were restricted to one side. After such a bilateral operation the author has frequently noted evidence of thrombosis become manifest later in the opposite leg, even though the superficial femoral vein had been interrupted some days previously.

In Table III are presented data on the mortality of thromboembolism complicating early, accelerated and delayed activity, treated both by conservative measures, and by femoral section and ligation. From this tabulation it is apparent that the mortality

of postoperative thrombosis is by no means eradicated by early and accelerated activity but the incidence of fatalities is definitely reduced. Although the number of patients treated by interruption of one or both femoral veins is small, the absence of fatal embolism after this type of therapy is significant and doubtless plays some rôle in the reduced mortality of thromboembolism after early and accelerated activity.

Data from which the over-all mortality in the entire group of 1,519 patients has been computed are included in Table II but have no bearing on the title of this paper and require no discussion.

ADJUNCTS TO EARLY AMBULATION

In all non-urgent operative procedures prophylaxis against thromboembolism during the convalescence should begin before the patient enters the hospital, continue during the operation, and be maintained with intensive vigor and meticulous care during the early postoperative period.

Preoperative. Reduction of weight if the patient is obese, correction of anemia if the hemoglobin and erythrocytes are below normal, injection or surgical eradication of major varices in the lower extremities, medical supervision of cardiac abnormalities, adequate amounts of carbohydrate and fruit in the diet³ and normal physical activity are important preoperative adjuncts to early postoperative ambulation if time permits. Eventually patients may be asked to prepare for the physical ordeal of elective surgery with much the same intent that athletes train themselves for events of physical stress, namely, to develop fitness and a reserve of energy adequate for the occasion and for the prompt restoration of normal activity thereafter.

Operative. Numerous and varied circumstances may contribute to the evolution of postoperative thrombosis; to enumerate them would be but to repeat the statements

of other authors, many of which have been copied from one by another without verification and have no scientific basis in fact. Very little careful and well controlled investigation of the etiology of thrombosis has been conducted and the cause of intravascular clotting is, even today, completely obscure.

Generally accepted by most authorities are (1) the probability that postoperative thrombosis usually originates in the large veins and venous plexuses in the calves of the legs,⁴ (2) that slowing of the circulation in the lower extremities, particularly retardation of the venous return, incidental to life in bed, is an important predisposing factor and (3) that the complication is more common during the later decades of life.

Since the ages of patients who require operative treatment cannot be regulated, prophylactic efforts against thrombosis during operation and the immediate convalescence thereafter must be directed toward the prevention of trauma to the deep veins of the legs when the patient is on the operating table and to stimulation of the venous circulation in the lower extremities after the operation has been completed.

The muscles of elderly patients are atrophic and those of younger individuals become flabby under anesthesia; the calves of both are easily compressed by contact with the firm, hard mattress of the operating table. Mechanical compression is readily transmitted to the deep veins of the legs, the vessels are collapsed, intimal surfaces are approximated and vascular injury may result, at least in theory. In order to obviate this contingency the author has a small pillow placed beneath the patient's thighs, of a thickness sufficient to cause slight flexion at the knees, to raise the calves just off the mattress and thereby eliminate pressure on the posterior surfaces of the legs during the operation.

Protection of the edges of the wound, care

in the placement of abdominal and pelvic retractors, gentle manipulation of tissues, accurate hemostasis, strict asepsis and maintenance of an adequate blood pressure are of acknowledged and obvious prophylactic importance.

Postoperative. When the unconscious patient is returned to bed he should be placed in a semiprone position, again to obviate pressure on the posterior aspects of the legs, and also to avoid aspiration of mucus and vomitus before consciousness returns. Immediate and continued elevation of the foot of the bed 8 inches from the floor will accelerate the flow of venous blood from the lower extremities as will also frequent and regular exercises for the feet and legs which should have been explained in detail to the patient before operation. A large sign, black letters on white cardboard, attached to the foot of the bed and always in view, will serve as a constant reminder of their importance.

Some unpublished studies by Dr. Brantley Holt and the author suggest that the venous circulation in the lower extremities of elderly patients responds less well to elevation of the foot of the bed and exercises of the feet and the legs than does the circulation of younger adults, an observation which may serve to explain the greater frequency of thrombosis and embolism among patients after the age of fifty years. The prophylactic value of turning from side to side, deep breathing, coughing, the avoidance of tight dressings and binders, the elimination of Fowler's position, adequate hydration and many other postoperative adjuncts to early ambulation have been advocated by numerous writers and need not here be repeated.

However, one further prophylactic measure which has not previously been stressed is of considerable importance. Elderly patients should not be allowed to "dangle" nor to sit in a chair with knees flexed and

legs and feet dependent. When such a patient is sitting out of bed the legs should be horizontal, the *heels only* supported on a soft footstool, the *calves* in contact with *nothing*. The muscles and veins are not then subject to compression and possible vascular injury which might conceivably predispose to thrombosis.

CONCLUSION

In reality most postoperative patients are normal, healthy individuals with aseptically sutured, cleanly healing wounds. Exercises in bed, ambulation within the first twenty-four hours, prompt resumption of a normal diet and a generally accelerated convalescence permit an early return to

customary activity. Unfortunately they do not favorably influence the incidence of postoperative thrombosis nor eradicate the hazard of pulmonary embolism.

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Treatment of Thrombophlebitis

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students, and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. WM. DEWITT ANDRUS: The subject of the conference today is the treatment of thrombophlebitis. This disease has been a source of a great deal of worry and annoyance to clinicians and is the cause of a great many tragedies. It is encountered in both medical and surgical cases. It is, therefore, of interest to all of us. The discussion will be opened by Dr. Irving Wright.

DR. IRVING WRIGHT: I may preface my remarks by saying that the treatment of thrombophlebitis constitutes one of the most controversial subjects in the field of medicine today, just as it has been for the last fifteen years. We have tried to steer a course between the two extremes, on the one hand, of prejudice and resistance to new advances in therapy and on the other, of overenthusiastic acceptance of therapeutic measures which have not seemed especially sound. Such a course has been quite difficult. Numerous forms of treatment have been suggested, many of which have enjoyed only temporary popularity. There was, for example, the plan of immediate ambulation without any supplementary measures such as venous ligation or anticoagulant therapy. The use of leeches was widely advocated abroad for many years, and to a lesser degree in this country. Lumbosacral block was advocated as a cure, and although it has proven to be of value in some patients, it is no longer regarded as a cure.

Thrombophlebitis is not a single disease.

There has been an unfortunate tendency in recent years to confine the scope of discussions on this subject to thrombophlebitis in postoperative patients and further, to thrombophlebitis of the lower extremities. There are many important types of the disease. There is the one due to chemical irritants, such as arsphenamine and concentrated vitamin C solutions. Another type is due to chronic trauma, for example, persistently tying shoe laces too tightly over the arch of the foot. There is suppurative thrombophlebitis in which the infection extends from a nearby abscess or severe infection. There is thrombophlebitis associated with various blood dyscrasias, such as polycythemia and leukemia. There is the type associated with thrombo-angiitis obliterans. Frequently, it is the presenting problem in thrombo-angiitis obliterans, the underlying disease escaping recognition by the physician. There is also thrombophlebitis migrans which is relentless and frequently spreads to all parts of the venous system, ending fatally in a high percentage of patients. It is evident that the treatment of thrombophlebitis cannot be reduced to a simple routine. The treatment of each patient must be decided on the basis of the etiologic factors and the presenting pathologic changes.

In any large hospital, the largest numbers of cases of thrombophlebitis are secondary to surgical or obstetrical procedures, but in

office practice and the practice of internal medicine one frequently sees cases due to the other causes.

The difference between thrombophlebitis and phlebothrombosis has received considerable emphasis, perhaps more than it deserves. It is true that thrombi in phlebothrombosis are not fixed firmly to the walls of the veins during the early days when there is little inflammatory reaction. In most instances as time elapses they become firmly fixed and cannot be distinguished pathologically from thromboses due to thrombophlebitis. The important matter is that venous thromboses, except those due to thrombo-angiitis obliterans, are capable of producing emboli. The silent thromboses frequently produce emboli as devastating as the ones that are easy to recognize. It is impossible to predict whether or not a patient who has a thrombophlebitis in the legs is going to have a fatal pulmonary embolus; therefore, all thrombophlebitis must be regarded as serious and potentially fatal if steps are not taken to prevent the formation of emboli.

Let us consider briefly the several therapeutic measures which have long been studied, although in the case of some of them considerable doubt still prevails regarding the best procedure. I believe there is a fairly universal agreement today that, in the case of a patient with thrombophlebitis of the lower extremity with edema, elevation of the extremity is helpful in reducing the edema to a minimum. To keep the affected extremity in a dependent position or at the level of the body is of no therapeutic value and may actually be harmful.

Whether heat or cold should be applied to such patients has long been debated. The consensus at present seems to favor heat, if properly applied. I am not sure that we know how to apply it properly. The technic described by Barker is now most acceptable. The affected extremity is carefully covered

with a thin layer of petrolatum or similar substance to prevent maceration of the skin and a moist, hot pack is applied. This may be in the form of turkish towels dipped in hot water, wrung out and laid loosely around the extremity which is then covered with a rubber blanket and surrounded by hot water bags. The hot pack is kept on for twenty out of twenty-four hours, allowing four hours for aeration and drying of the skin. In severe cases with marked edema, both lumbosacral sympathetic block and hot packs may be used simultaneously. The application of hot packs to an extremity immediately after lumbosacral block seems to prolong the vasodilating effect of the block, reducing vascular spasm and permitting more free drainage.

The matter of activity versus rest has long been debated and it is still unsettled. There were some who believed that one should wrap a bandage tightly around an affected leg and instruct the patient to walk forty or sixty blocks a day, if there were no symptoms. I have seen some very poor results from this form of therapy. There are those who believe in keeping the patient at complete rest in bed until signs of the disease have completely subsided, as determined by the return to normal of the sedimentation rate, blood count, heart rate and temperature. A middle course between these two extremes seems to be the present tendency. Those who have been using anticoagulant therapy have been allowing their patients up earlier, keeping them in bed between six and ten days rather than twenty-eight or thirty days.

The control of epidermophytosis is a point of very great importance in those patients with the idiopathic type of thrombophlebitis. Some believe that there is a very close causal relationship between fungus infection and thrombophlebitis of the lower extremities, either allergic or by direct

invasion of the vein by the infectious agent. Also, the fungus produces cracks in the skin which facilitate entry of secondary invaders. In many patients who have had thrombophlebitis repeatedly, recurrences are apparently prevented by the simple expedient of keeping the dermatophytosis under control.

There is one point, the importance of which I cannot emphasize too strongly, namely, that of refraining from making physical examinations of the chest in which patients are instructed to take deep breaths for the purpose of determining whether or not an infarction of the lungs has taken place or the location of the infarct. Deep breathing increases the negative pressure in the chest, thereby increasing the speed of blood flow from the extremities and which may break off the loose tails of the thrombi. If a person was operated upon ten days previously or if he has an acute phlebitis and suddenly develops a stabbing pain in the chest and coughs up some blood, it is quite probable that he has developed a pulmonary embolus. It is of minor importance to learn exactly where the infarct is. It is purely an academic question. There have been several deaths following shortly upon such examinations. So far this dangerous procedure has received only brief mention in the literature. Sliding an x-ray cassette under the patient's chest is a much safer way of locating an infarct.

A patient should also be advised against violent coughing and straining at stool, and it is up to the doctor to see that the patient does not indulge in either. There have been a number of patients with thrombophlebitis who have died during defecation. I knew one patient who died under these circumstances a month after she was discharged from the hospital, at a time when the thrombophlebitis appeared to have subsided completely.

Venous ligation as an aid in treating thrombophlebitis has had a troubled his-

tory. It appears as though its exponents have been chasing the rainbow's end from the lower saphenous vein all the way up to the superior vena cava. One of the shortcomings of treatment by ligation is that emboli may result from thrombi forming at the site of any ligation. Thrombophlebitis and varicosities also sometimes recur after ligation of the affected vein. I have a patient in the hospital now who never did have an embolus from the original thrombophlebitis, but promptly after a bilateral femoral ligation she began to have emboli and continued to have them until treated with anticoagulants. Edema may also sometimes occur following ligation. It is maintained by the exponents of ligation of the inferior vena cava that following this procedure there is less edema than is seen after femoral ligation, but on reading the reports of a few years ago one sees that some enthusiasts then maintained that there was no edema following femoral ligations. I believe there are specific indications for ligation but this procedure should not be used indiscriminately. It is indicated if there is a lesion in a lower extremity which gives rise to recurring emboli. Ligation is a much safer procedure now that anticoagulant therapy is available and anticoagulant therapy should always be used following venous ligation. Varicose veins, of course, constitute the major field for ligation and no one can dispute the importance of the operative procedure in these cases.

Now we come to another subject of considerable controversy, namely, anticoagulant therapy. Heparin was the first of the chemically effective anticoagulant agents. We have followed its use with great interest since it became available in this country for the treatment of thrombophlebitis. It prolongs the coagulation time. Statistics clearly show that it markedly reduces the number of pulmonary emboli and the number of deaths. It is administered, as most of you

know, either by continuous intravenous infusion so as to keep the coagulation time preferably between twenty and forty-five minutes, or by repeated intravenous injections of 75 mg. every three or four hours. This method produces marked fluctuations in the coagulation time, as high as one hundred minutes shortly after the injection, with a return to normal before the next injection. Dr. Loewe has been developing a menstruum which releases heparin slowly. The present menstruum for an intramuscular injection cannot be considered entirely satisfactory; its injection is extremely painful to the patient, it is difficult to control and it produces nausea in some patients, but I think it is a move in the right direction and the subject should be pursued further. There are many disadvantages in the use of heparin. It is an expensive procedure. So far, it can be administered only by injection and the danger of hemorrhage from improper use is well known. It requires close supervision by the house staff both day and night for the duration of its administration in order to check the blood coagulation time, although with the intermittent method the number of checks of coagulation time is reduced markedly.

Dicumarol has now become more popular. It is inexpensive. It can be given by oral administration. Dicumarol interferes with the production of prothrombin and it affects the coagulation time. There has been some question about the effect of dicumarol on the coagulation time and unless the test is properly made one may fail to detect a prolongation of the coagulation time. In this connection a word should be said about the Lee-White glass tube method. Some important work has recently been undertaken in a number of institutions to study the types of tubes other than glass, because it has long been recognized by those of us working in the field of peripheral vascular diseases that the glass tube Lee-White method does not

even remotely represent coagulation time as it occurs in the blood vessels. I should like to quote some hitherto unpublished figures from Dr. Kadish of the Mayo Clinic. Using the Lee-White method he found the coagulation time from six to seven minutes with the glass tube, from thirteen to fourteen and even up to nineteen minutes with the lucite tube and considerably higher values with the collodion or paraffin tube. With the lucite tube the normal value of thirteen to nineteen minutes is found shortened to six to eight minutes in those patients with thrombophlebitis and prolonged to thirty to forty minutes or more in a patient taking dicumarol. Even with the glass tube, if the test is carefully performed, it can be shown that dicumarol prolongs the coagulation time but the use of the lucite tube provides a much more sensitive method for demonstrating this change. In our laboratory, however, the results with the lucite and other tubes have been too unpredictable to be used as a guide to dicumarol dosage.

Dicumarol therapy also has several disadvantages. It requires daily prothrombin tests and the laboratory must be prepared to do them. It is difficult to get laboratories to do the test accurately. As with heparin there is the risk of hemorrhage if the patient is not watched carefully. There are several gaps in our knowledge of the action of dicumarol. Work on intravascular clotting in animals is not sufficient, so our knowledge of the action of dicumarol has to advance largely by cautious experiments on man.

There are some very striking figures on the value of dicumarol therapy. One might mention those of Barker and his group at the Mayo Clinic in which they compared the results in 897 patients with thrombophlebitis treated without anticoagulant agents before emboli developed, with the results in 138 similar patients treated with dicumarol. An incidence of 10.6 per cent of subsequent thrombophlebitis or pulmonary embolism

was reduced to 2.9 per cent in the group with dicumarol; also, an incidence of 5.7 per cent of fatal pulmonary embolism was reduced to 0 per cent in those treated with dicumarol. They also made another type of analysis. They compared the results in 678 patients who had suffered one or more non-fatal embolus and did not receive anticoagulant therapy, with the results in 180 similar patients treated with dicumarol. An incidence of 43.8 per cent of subsequent thrombosis or embolus was reduced to 1.1 per cent in those treated with dicumarol; also, an incidence of 18.3 per cent of fatal pulmonary embolus was reduced to 0.6 per cent in those treated with dicumarol. It is noteworthy that substantially similar results in very large groups of patients have been reported by Jorpes and his collaborators from the Karolinska Institut in Stockholm, where they used heparin in some patients and dicumarol in others.

DR. ANDRUS: As Dr. Wright has pointed out the therapy of thrombophlebitis is complicated and none of the various methods of treatment which have been used in the past have been entirely satisfactory, but certainly a great advance has been made with the use of anticoagulant therapy. I think that perhaps the internists and surgeons, while they see the problem from a common point of view in many ways, look upon certain aspects of it somewhat differently. I will ask Dr. Glenn to discuss this problem from the surgical point of view.

DR. FRANK GLENN: To the surgeon, pulmonary embolism is always a matter of grave concern and the surgeon's attack on it must begin with the preoperative preparation of the patient and the care of the patient during the operation.

It seems to me that the care which has been exercised in the operating room in the past few years to maintain an individual's blood pressure at a proper level has been of great importance in reducing the incidence

of postoperative thrombophlebitis. Permitting the blood pressure to fall to a low level and the associated shock certainly predispose to coagulation of blood, especially in the vessels of the lower extremity. The care of the patient after operation is equally important. Having the patient do exercises while in bed and employing early ambulation help to reduce the incidence of thrombophlebitis and emboli, especially those fatal emboli which arise from the lower extremity. Statistics from various laboratories of pathology show that the majority of these fatal emboli from the lower extremity arise from the deep femoral circulation. When conservative measures fail to prevent the appearance of emboli or thrombophlebitis the surgeon naturally tends to take more active steps.

There has been a great deal said about ligation. In our clinic here we do not follow in the footsteps of some of those farther up the coast who even do prophylactic ligation. Nevertheless, when one is confronted with what appears to be a thrombophlebitis with embolism, interruption of the deep circulation is certainly indicated. It should be undertaken immediately. Where one may limit treatment to the use of anticoagulant therapy alone, especially in the surgical cases, is a question that has certainly not been settled.

In tracing the history of ligation one finds that the first approach involved ligation of the superficial circulation. Division of the deep femoral circulation was not attempted until later. For the majority of patients the division of the deep femoral vessels is probably the procedure of choice. I certainly believe that following ligation of these vessels the incidence of emboli has been reduced. Along with the interruptions of the deep femoral circulation, anticoagulant therapy as already outlined, is certainly indicated. Some object to operative procedures because of the edema and disability

which may result. Generally speaking, we have found that division of the deep femoral circulation is not followed by as much edema as one is led to believe. Usually, the higher the interruption of the venous return the better is the collateral circulation which is thereafter established. If a patient has been ill for a long time or has had some surgical procedure involving one extremity and thrombophlebitis has developed, then the choice rests between a bilateral ligation of the femoral and the common iliac vessels. In patients with pelvic involvement ligation of the inferior vena cava is indicated. This is an heroic procedure and is occasionally fatal but I believe it can be utilized to good advantage if combined with anticoagulant therapy.

DR. ANDRUS: The topic today is the treatment of thrombophlebitis but I am sure that all of those interested in the subject agree that the most important aim is the prevention of thrombophlebitis. Unfortunately, our understanding of the factors which produce it is very meager. However, I think that we do know of certain measures which tend to diminish the incidence of thrombophlebitis, such as the avoidance of infection, the prevention of stasis in the veins of the legs resulting from the use of tight dressings, from distention of the abdomen or from the low blood pressure of shock. The use of deep breathing exercises prophylactically after operation has been widely employed, as well as the use of routine postoperative exercises with the patient in bed until early ambulation is feasible. Deep breathing is used to prevent venous stasis. It is certainly to be carefully avoided if thrombophlebitis is present or even suspected. No methods of prevention are universally successful. It is to be hoped that continued investigation will give us greater understanding of this complicated group of diseases and will reveal more effective means of prevention and better therapeutic agents.

Dr. Wright, will you make a few remarks on the diagnosis of thrombophlebitis? How do you demonstrate its presence?

DR. WRIGHT: I wish to say first, that I agree with Dr. Andrus in that if we keep these individuals active, get them out of bed very early, move their legs, have them exercise in bed and take deep breathing exercises the number of thrombi that will be available for pulmonary emboli will probably be markedly reduced. The diagnosis of most cases of thrombophlebitis is usually relatively easy. One of the first symptoms is pain, which is frequently along the course of a vein. One can usually see some redness along the course of the vein and detect tenseness on palpation. Sometimes the vein is still patent but often the lumen is obliterated quickly by thrombus. Sometimes there are cramps in the muscles and there is usually fever, tachycardia and increased sedimentation rate. Those are all cardinal signs; however, many patients complain of only vague pain in the calf and Homans' sign is equivocal. This sign is considered positive when pain is produced in the gastrocnemius area as the result of dorsiflexing the foot by pressure on the distal portion of the sole of the foot with the patient in the supine position. A positive sign is suggestive of thrombophlebitis, although other conditions such as strains and injuries of the soleus muscle may simulate it. The amount of pain may depend on how hard the examiner presses against the ball of the foot because one can produce pain in a normal soleus muscle by overtaxing it. I am sure there are some false Homans' signs elicited by too strenuous dorsiflexion of the foot but at any rate one must watch for the minimal signs. There are patients with marked thrombosing processes and fatal embolisms in whom there are no signs prior to the emboli.

DR. ANDRUS: As Dr. Wright said, whether a patient with thrombophlebitis should be

kept quiet or should be active has been the subject of a good deal of difference of opinion. You may be interested in the story which was told about Dr. Bloodgood at Johns Hopkins. He preached to his students most assiduously that all patients with thrombophlebitis should be kept perfectly quiet. He himself, in the course, I think, of a pneumonia for which he was treated at home, developed a thrombophlebitis. During sleep he fell out of bed and spent the next ten days on the floor, refusing to be moved. At least he was consistent and had the courage of his convictions. Dr. Wright mentioned that some compromise might be reached between complete quiet and early activity. Would you care to say a little more about where the compromise should be made?

DR. WRIGHT: In the light of our present knowledge I should say that the patient should be kept quiet until he is under adequate anticoagulant therapy. Experience at the Mayo Clinic and in Sweden indicates that these patients may be allowed out of bed with very little risk, within five days after adequate anticoagulant therapy has been established.

A word about what we consider adequate therapy. With heparin, I think, a prolongation of the coagulation time to between twenty and forty-five minutes is adequate. It is much safer than if it is allowed to go up to seventy-five minutes. Beyond this a dangerous level is reached very quickly. We have had very satisfactory results in some hundreds of patients, with the coagulation time no higher than forty-five minutes.

With dicumarol we seek to maintain the prothrombin time between thirty and fifty seconds which with the technic we use is between 20 and 10 per cent of the normal prothrombin activity. That seems to be an adequate range. Some workers believe that the anticoagulant effect is satisfactory only if the prothrombin activity is lower than 20

per cent but there is no satisfactory proof that so much depression of prothrombin activity is necessary.

DR. GOLD: Perhaps a word should be said here about the meaning of the terms "prothrombin time" and "prothrombin activity." There is a good deal of misunderstanding about them. The prothrombin content of the blood is expressed as "prothrombin activity." This may be greatly reduced before there is any striking change in blood clotting. Since the test for "prothrombin time" depends on speed of clotting this test becomes abnormal only after considerable reduction has taken place in the prothrombin content of the blood. In actual testing of the "prothrombin activity" using blood dilutions (which are in effect the same as reducing the concentrations of prothrombin) it has been found, for example, that by the time the prothrombin content has been reduced from 100 to as low as 30 per cent of the normal, clotting has been only moderately impaired as shown by the fact that the "prothrombin time" has only risen from about twelve to eighteen seconds, or a rise of only about 50 per cent. Beyond a given point, however, further reduction in the prothrombin content (prothrombin activity) begins to influence greatly blood clotting (prothrombin time) and small further reductions in the content of prothrombin begin to produce large increases in the prothrombin time; for example, a reduction of the prothrombin activity from 30 to 10 per cent of the normal, delays clotting so much that it raises the prothrombin time from 18 to 38 seconds, that is, a rise of about 100 per cent. The point of this is to emphasize the need for bearing in mind the difference between the terms "prothrombin activity" and "prothrombin time." The further point is that after a conspicuous rise in prothrombin time has taken place with dicumarol therapy, the patient must be watched carefully, for small addi-

tional doses of the drug by causing further small reductions in the prothrombin content, may produce abrupt rises in the prothrombin time, blood clotting being so markedly impaired as to give rise to spontaneous hemorrhages.

In the actual carrying out of the test for the prothrombin time in the laboratory, there appear to be so many variables that it is necessary to have a control subject tested at the same time, as a means of insuring the accuracy of the test. It might be well for the physician to consult with the laboratory which performs the prothrombin test for him, in order to be sure of the precise meaning of the figures which are reported to him since the results obtained by different laboratories are somewhat different depending on the conditions of the test.

I should like to ask Dr. Wright what percentage of bed patients who develop a pulmonary embolus give evidence of thrombophlebitis prior to the embolus.

DR. WRIGHT: I do not know of any adequate figures on that point. Perhaps some of the surgical staff can answer the question more specifically.

DR. ANDRUS: After an embolism occurs you can nearly always determine where it came from, but I know of no figures on the number of patients in whom the diagnosis of thrombophlebitis is made or is possible before emboli have occurred.

DR. HAROLD E. B. PARDEE: In relation to Dr. Gold's question I think it is only in a small percentage of patients in whom one recognizes signs of thrombophlebitis prior to the embolic phenomena.

DR. GOLD: I agree with that. I have seen many cases of pulmonary embolus in non-surgical patients but I can recall only two instances in which signs of phlebitis presented themselves prior to the embolus, to suggest the possibility of embolus. It may be that the signs of thrombophlebitis are often not very conspicuous and we do not

look carefully enough in medical patients confined to bed.

DR. ANDRUS: I would certainly claim no special ability for the surgical service, for I know there are many patients in whom we recognize the thrombophlebitis only after the embolus but there are certainly a great many in which we recognize thrombophlebitis beforehand. I would guess that we recognize the phlebitis in about half of the patients before they have an embolus.

DR. WRIGHT: Do you not think that that represents a very strong teaching point, namely, our house physicians should be trained to make daily observations post-operatively on the legs of all patients? I am sure that many more of these cases would be recognized if that were a standard procedure on all surgical services.

DR. PARDEE: How long do you believe anticoagulant therapy should be continued and what criteria would you use for stopping it?

DR. WRIGHT: It depends on the type of case. We like to keep the individual who has had a simple thrombophlebitis of short duration on anticoagulant therapy for three to four weeks. I have recently been told that at the Mayo Clinic they continue dicumarol therapy for only eight to ten days and that their results have not changed with this brief therapy. We have perhaps been playing overly safe. However, we see a considerable number of patients who have thrombophlebitis for from four months to three years almost without interruption. The phlebitis is sometimes migratory and sometimes largely localized to one set of veins. It seems desirable to keep these patients on anticoagulant therapy for four weeks at least. Such prolonged treatment has been strikingly successful in interrupting chronic phlebitis.

STUDENT: How do you manage the post-operative patient who develops a hemorrhage while on the anticoagulant therapy?

DR. ANDRUS: The first thing is to discontinue the anticoagulant. By giving massive transfusions and massive doses of vitamin K, the hypoprothrombinemia associated with dicumarol can be corrected to a degree. For hemorrhage occurring during the use of heparin, protamine has been suggested for neutralizing the heparin but its use is still in the experimental stage. Transfusions are also useful.

DR. GOLD: Cromer and Barker gave a single intravenous dose of menadione bisulfite (a synthetic vitamin K), 64 mg. (4 mg. per cc.) to a group of patients in whom dicumarol had produced excessive prolongation of the prothrombin time to such levels as eighty-five seconds or more, and fairly regularly obtained a prompt lowering of the prothrombin time. The result appeared in about two hours and reached a maximum in about eighteen hours. These doses of vitamin K are harmless.

DR. WRIGHT: The risk of hemorrhage in these patients is very slight, if the prothrombin time is accurately tested and the daily dose of dicumarol is withheld until the prothrombin level for that day is known. We have treated, or supervised the treatment with anticoagulants of more than 800 patients. We have had people die of carcinoma or progressive thrombophlebitis migrans but we have not had, so far, a single patient die of hemorrhage from dicumarol. In the recently operated surgical case, of course, the risk is greater. It is customary at the Mayo Clinic to start dicumarol therapy on the second or third day postoperatively in order to lessen the danger of hemorrhage.

VISITOR: How long do you continue the dicumarol after the patient is ambulatory?

DR. WRIGHT: We continue the patients on anticoagulant therapy after we get them up and about. We may keep them ambulant in the hospital for an extra week or ten days. It is like having a bear by the tail. We do not know exactly when to let go.

VISITOR: Is the treatment with dicumarol stopped abruptly?

DR. WRIGHT: We usually find it desirable to taper the dosage down gradually over several days. With an intelligent and co-operative patient it is sometimes possible to continue the dicumarol with the patient ambulant outside the hospital, having him go to a laboratory for tests of the prothrombin time.

DR. JANET TRAVELL: How often are these patients checked and how much dicumarol do they receive?

DR. WRIGHT: Most of our present ambulatory patients receive approximately 600 mg. a week in doses of 100 mg. daily; the dose is omitted on Sunday. That seems to be adequate for most patients. Whenever possible we have the prothrombin time checked daily or every other day and, of course, the dose is omitted on any day when the prothrombin activity is below 15 per cent of the normal.

DR. ANDRUS: How predictable is the effect of a given dose of dicumarol in a given individual?

DR. WRIGHT: In general, I believe that after a patient receiving dicumarol has been under observation for a period of two or three weeks, one learns enough about that patient to predict fairly accurately what the effect of a dose will be. However, the susceptibility of individuals varies greatly and it is unsafe to predict the effect of a dose at the start of therapy. Every once in a while an article appears recommending 1,000 mg. of dicumarol as the first dose. Such dosage is extremely dangerous. One may give 300 mg. as the first dose relatively safely, and 300 mg. on the second day, then tapering off gradually to 200 mg., and 100 mg. daily. If that dosage system is accompanied by a careful daily check of the prothrombin time, I do not think one will get into trouble very frequently but one may anticipate some minor hemorrhages.

Before we close this discussion I think I should say a word about the care of the patient after he recovers from the acute thrombophlebitis. Such care is one of the most important, but also one of the most neglected, phases of the management of this disease. We must remember that thrombophlebitis can be arrested but it should never be regarded as cured. Most of these patients have pains when they stand a long time and when the barometer changes. They worry about these pains and many of them become psychoneurotic because they never know whether the pain presages another attack of phlebitis. The neglect of proper prophylactic care increases the tendency of edema, ulcers and varicose veins. We can prevent these unfortunate sequelae by several means. It was found that a group of patients wearing knee length, well made, individually fitted elastic stockings for the first year after their thrombophlebitis had at the end of five years far less edema, far fewer pains and far fewer ulcers of the legs than those patients who went without stockings. I think that the use of such stockings is very important. It is essential to instruct the patient on how to prevent dermatophytosis. It is also most necessary to explain to the patient that pains in the legs do not always mean a recurrence of the thrombophlebitis. Fear of a recurrence may be one of the most serious disabilities. We have seen patients who, five years after the attack, are fearful of moving about or unnecessarily restrict their activities because they fear that when they have a pain in their leg they are on their way to a recurrence. This reaction is understandable in people who have passed through two or three attacks. We have formulated some arbitrary rules which have proved helpful to these patients. If the pain lasts less than an hour they should ignore it, for most of these pains last less than fifteen minutes. If it lasts one to three hours, they should lie down and elevate the feet or get into a tub

of cool water, which frequently gives relief. If it lasts more than three hours, they should call their physician. Most of them will say, "Well, now that I know I don't have to worry about pain that lasts less than an hour, I go ahead and do what I want to do and have stopped worrying about it." There is the fact that some pains may recur for several years after an acute attack, and the patient's failure to understand this may result in much needless physical and psychoneurotic invalidism.

SUMMARY

DR. LAWRENCE W. HANLON: Some of the problems of treatment of thrombophlebitis were explored this afternoon. There are many varieties of thrombophlebitis differing in their causes, clinical aspects and pathologic changes. The regimen of treatment should be adjusted to the special requirements of the particular patient. The differentiation between phlebothrombosis and thrombophlebitis has limited value, since after a time, the thrombi in the two become pathologically indistinguishable. While thrombophlebitis often makes its appearance with characteristic signs and symptoms, such as pain, tenderness, swelling, fever and elevated sedimentation time in many of these patients the onset is silent and the first indication of the disease is a pulmonary embolus. Emphasis was placed on the desirability of making routine systematic examinations of the legs in surgical and non-surgical patients confined to bed, as a means of uncovering cases of thrombophlebitis sufficiently early to make it possible to prevent pulmonary complications.

The discussion covered measures that are useful in the prevention of thrombophlebitis, such as care against traumatization of vessels, prevention of infection, control of epidermophytosis, free movement in bed, early ambulation, deep respiratory exercises and the avoidance of the latter in thrombo-

phlebitis to prevent pulmonary embolism. Attention was called to the highly controversial nature of the measures used in the treatment of thrombophlebitis; the application of heat and cold, the use of leeches, prolonged rest, free exercise, early ambulation, dependent and elevated position of the extremity, lumbosacral sympathetic block, prophylactic venous ligation and the use of anticoagulant agents. It was indicated that the consensus favors hot, moist packs to the affected extremity, the elevated position of the limb to control swelling, a middle course in relation to rest and activity, the patient being allowed up and about after a short period of rest even though the disease is not fully checked provided anticoagulant therapy is employed. There are those who recommend prophylactic ligation of the veins in thrombophlebitis of the lower ex-

tremity in order to prevent embolism, although others prefer a more conservative course, ligating only after there is proof that the vein is a source of recurrent embolization. The choice of site for ligation depends on the location of the phlebitis.

The use of the anticoagulant agents, heparin and dicumarol, appears to be an advance of the first importance in the treatment of thrombophlebitis. Figures were cited showing most extraordinary results following their use; for example, second thrombosis or embolus was reduced from an incidence of nearly 50 per cent to about 1 per cent, cases of fatal pulmonary embolus with an incidence of nearly 6 per cent completely vanished. The discussion embraced the details of application, dosage, mode of action, dangers and methods of control of anticoagulant therapy.

Clinico-pathological Conference

Gastrointestinal Disease with Hematemeses and Hepatic Insufficiency*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a thirty-seven year old Negro Pullman porter who entered the Washington University Clinics on November 22, 1946, complaining of indigestion, nausea and vomiting. The family history was irrelevant. The patient had had Neisserian infection twice; both times he recovered uneventfully. He had an occasional hacking cough, productive of blood-streaked sputum, and stated that his gums bled easily, apparently because of poor dental hygiene. Although his diet seemed adequate, he took a moderately large amount of alcohol. There was no history of ingestion of drugs or contact with heavy metals.

He was quite well until seven months prior to his admission to the Clinic when he developed a sensation of fullness in the upper abdomen after meals, usually associated with considerable abdominal distention and especially noted after the ingestion of fatty pork. He usually vomited almost immediately after eating but occasionally one to one and one-half hours later. He consulted a physician who prescribed medication of an unknown type, and was then relieved until four weeks before entry when again after eating fatty meat, he developed abdominal distention, nausea and vomiting. Subsequently he had moderately severe burning distress in the upper abdomen

occurring usually at night; it was relieved by milk but only questionably by alkalis. He vomited three to four times daily and four days before coming to the Clinic noted bright red blood in the vomitus. During the first and second episodes of abdominal pain, the patient thought his urine had become darker than usual. Five days before coming to the Clinic he developed generalized pruritus. Although he had felt feverish, he had not taken his temperature.

Examination in the Clinic revealed the vital signs to be normal. The patient was well nourished and well developed but appeared somewhat ill. The skin was dry but there was no apparent weight loss. The sclerae were icteric; the pupils reacted well to light and accommodation and the fundi showed only slight arteriolar narrowing. Examination of the mouth revealed marked pyorrhea. The tonsils were large and the pharynx red. The heart and lungs were normal. The liver edge was rounded and was felt 4 cm. below the right costal margin. The spleen could not be palpated. The prostate gland was normal and no neurologic findings of significance were described.

The laboratory studies were as follows: Blood count: red cells, 5,760,000; hemoglobin, 15.3 Gm.; white cells, 8,600; differential count: stab forms, 6 per cent;

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

segmented forms, 65 per cent; lymphocytes, 29 per cent. Urinalysis: albumin, very faint trace; bile, negative; sediment, negative. Stool: guaiac negative. Blood Kahn test: negative. Icteric index: 21. Hippuric acid test: 33 per cent excretion of sodium benzoate. Gastrointestinal roentgenograms: "The gastric motility is adequate. The duodenum shows a marked pressure narrowing of the proximal second portion with a fine longitudinal relief pattern not indicating an intrinsic but rather an extrinsic pressure deformity, apparently from the pancreas." Cholecystogram: "The gallbladder could not be visualized."

While the gastrointestinal x-rays were being made, the patient vomited about one-half cup of bright red blood, and on December 3, 1946, he was admitted to the hospital.

On admission, the only significant change in the physical examination from those previously recorded was the presence of a Grade II systolic murmur in the third and fourth interspaces. Laboratory studies included a red cell count of 3,560,000 with 13.5 Gm. of hemoglobin. The urine was positive for bile and urobilinogen was present in a dilution of 1:20 but not of 1:40. Other laboratory findings included the following: cephalin-cholesterol flocculation test: 3+; alkaline phosphatase, 12 Bodansky units; icteric index, 90; Van den Bergh test: direct, 4.5 mg. per cent; indirect, 2.3 mg. per cent; serum amylase, 112 units; cholesterol, 198 mg. per cent; prothrombin time, 75 per cent of normal; total proteins, 6.3 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 3.5 Gm. per cent.

On the day following admission the patient vomited 400 cc. of blood-streaked material. On examination at that time his abdomen was noted to be distended and tympanitic. Surgical consultation was obtained but no indication for operative intervention was apparent.

On the fifth hospital day urobilinogen

was present in the urine in a dilution of 1:80. The urine continued to be positive for bile as did the stool. Although he continued to vomit blood-tinged material occasionally, the patient took a restricted diet quite well. On the eleventh hospital day a second gastrointestinal x-ray series again showed no intrinsic abnormality of the duodenum but the same extrinsic pressure defect as reported in the earlier films. Two and one-half weeks after admission to the hospital the patient's abdomen became more distended and signs of ascites became apparent.

Laboratory studies at this time were as follows: The urine was positive for bile and urobilinogen was present in a dilution of 1:60. The stool was likewise positive for bile. Total protein, 5.5 Gm. per cent; albumin, 2.2 Gm. per cent; globulin, 3.3 Gm. per cent. Icteric index, 70. Van den Bergh test: direct, 4.5 mg. per cent; indirect, 2.27 mg. per cent. Cephalin-cholesterol flocculation test: 4+. Alkaline phosphatase: 12 Bodansky units.

On the twentieth hospital day the patient complained of sharp cramping pain in the mid-abdomen and epigastrium which was relieved somewhat by atropine. Shortly thereafter, he began to hiccough, and vomiting, which had subsided, recurred with production of a small amount of clear yellowish fluid. The temperature was 38.6°C., pulse 100, respirations 36, and blood pressure 120/70. The abdomen was markedly distended and tympanitic and there was dullness in the flanks. Although moderate tenderness was noted in the upper portion, there was no true spasm. A paracentesis was performed and 1,200 cc. of greenish-yellow fluid were removed. The specific gravity was 1.010 and there were 108 cells of which 90 per cent were mononuclear forms. The protein content of the ascitic fluid was 0.7 Gm. per cent. On culture the fluid was sterile. The red blood

count at this time was 5,000,000, the white count 7,900, and there was a slight left shift in the differential count.

The patient was again seen by a surgical consultant but it was not believed that operation was indicated. A Levine tube was passed and 150 cc. of brownish, thick fluid was obtained. Wangensteen suction was instituted but abdominal distention was not relieved. Because of the persistent elevation of the temperature and pulse, penicillin was begun in dosages of 40,000 units every three hours intramuscularly.

On the day following onset of abdominal pain the white count rose to 14,000 with 6 per cent juvenile forms and 80 per cent stab forms in the differential count. The icteric index was 80 and the non-protein nitrogen 25 mg. per cent. The patient was weaker and his abdomen remained distended. He complained of occasional sharp stabbing mid-abdominal epigastric pain. The temperature was again 38.6°C., the pulse 120, but the blood pressure had fallen to 90/60. An x-ray film of the abdomen was described as showing distention of the small bowel and questionable air beneath both diaphragms. The blood amylase on this occasion was 370 units per cent. A second paracentesis was performed three days after the first and 500 cc. of cloudy orange-yellow fluid were removed. The specific gravity was 1.014, the protein content 2.5 Gm. per cent, and there were 8,000 cells of which 55 per cent were polymorphonuclear forms. On culture coliform organisms were recovered. Streptomycin was given in dosages of 0.25 Gm. every three hours intramuscularly. On the day following the second paracentesis the patient's temperature was 38.4°C., pulse 130, respirations 24, and the blood pressure 90/70. He was unresponsive to questions; the heart sounds were of good quality and signs of bilateral pleural effusion, thought to be due to the high diaphragms, appeared. During the

course of the day the peripheral pulsations were no longer palpable and although the heart sounds continued to be of good quality, the blood pressure fell to 50/0. The extremities became cool. Following the infusion of two units of plasma the pulse rate was 134, respirations 34, and blood pressure 72/50. The patient continued to do poorly despite supportive therapy and his temperature rose to 39.2°C. He expired on December 27, 1946. During his hospital stay he received large amounts of choline, vitamins, and intrahepatol.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Seven months before his death this thirty-seven year old Pullman porter first had an episode of abdominal distress associated with nausea and vomiting. Within a few days he felt well and not until six months later did symptoms of gastrointestinal disease reappear. The second episode was characterized by abdominal distention, vomiting and burning epigastric distress. It would be well to inquire what lesion might produce such symptoms. Dr. Duden, would you comment on this point?

DR. CHARLES N. DUDEN: I saw this patient in the Clinic and subsequently in the hospital. At first, we were very puzzled as to the nature of the disease and when he was admitted to the hospital, we had made no specific diagnosis. Since the original discomfort apparently followed indiscretion in diet, and in view of the fact that the patient had an alcoholic history, it was believed that the entire symptom complex might have arisen as a result of his poor eating habits. Early Laennec's cirrhosis was considered, as was gallbladder disease, although it was believed that the patient was young for the latter.

DR. ALEXANDER: In other words, you considered that the vomiting originally may not have been due to an obstructive

lesion but rather that it may have been a reflection of cholecystitis or cirrhosis. Dr. Scheff, what is your feeling regarding the nature of this patient's illness?

DR. HAROLD SCHEFF: In my opinion, the two most likely possibilities are gall-bladder disease and peptic ulcer. The burning pain, coming on often at night and relieved by milk, certainly suggests the pain of peptic ulcer. I agree with Dr. Duden, however, that the patient had signs of Laennec's cirrhosis.

DR. ALEXANDER: He certainly had evidence of liver damage, particularly later in his course. When you spoke of gall-bladder disease, were you referring to cholecystitis?

DR. SCHEFF: Yes, I meant to imply inflammation of the gallbladder associated with biliary calculi. Since the patient was jaundiced, a calculus was probably in the common bile duct.

DR. ALEXANDER: Would you entertain the idea that esophageal varices, secondary to cirrhosis, gave rise to the hematemesis?

DR. SCHEFF: Yes, that is possible, but from the x-ray studies we know that there was an abnormality of the second part of the duodenum, and I have seen similar roentgenologic changes produced by an ulcer in that region.

DR. ALEXANDER: On two occasions, however, the radiologists interpreted the films as showing an extrinsic lesion. Dr. Bottom, do you think that an ulcer in the second portion of the duodenum could have given rise to the x-ray findings?

DR. DONALD S. BOTTOM: I think that very unlikely.

DR. ALEXANDER: May there have been an ulcer of the first portion of the duodenum?

DR. BOTTOM: Possibly.

DR. BRUCE D. KENAMORE: I believe compression of the second portion of the duodenum, as indicated by the roentgenograms, could have been responsible for all

of the patient's symptoms. Extrinsic pressure may occasionally produce hemorrhage by causing tension and rupture of the vessels within the duodenal wall.

DR. ALEXANDER: You are not attracted to the possibility that the patient had a duodenal ulcer?

DR. KENAMORE: No, I am not. I believe that he may have had a secondary erosion but that peptic ulcer was not the primary lesion.

DR. ALEXANDER: Are there other suggestions?

DR. JOHN R. SMITH: Those of us who saw the patient after his admission to the hospital considered duodenal ulcer as a very likely possibility. The question was raised as to whether the ulcer might not have perforated into the pancreas, giving rise to an inflammatory process which caused partial obstruction of the common bile duct and possibly of the pancreatic duct. The latter thought prompted the determination of the serum amylase.

DR. ALEXANDER: If the constriction of the duodenum was extrinsic, what lesion might be responsible?

DR. SMITH: One should consider the possibility of an annular pancreas.

DR. ALEXANDER: Is not such a lesion very rare?

DR. SMITH: I do not know the exact figures but it certainly does not occur very often.

DR. ALEXANDER: I believe Lehman assembled only forty-three cases in all of his study. Dr. Moore, how often have you seen an annular pancreas?

DR. ROBERT A. MOORE: I have seen only one.

DR. ALEXANDER: In annular lesions of the duodenum, are there symptoms other than those due to the obstruction?

DR. DUDEN: No, I do not believe so. I also am of the opinion that a duodenal ulcer was not the primary lesion. Another

possibility is a congenital deformity of the duodenum with subsequent development of an ulcer. A large cirrhotic liver or an enlarged gallbladder might have given rise to the roentgenologic findings, and conceivably a tumor at the head of the pancreas could likewise have done so.

DR. ALEXANDER: Dr. Wade, would you comment on the possibility of liver disease? Do you think the liver was seriously compromised?

DR. LEO J. WADE: I considered the possibility that the liver could have been responsible for the obstruction. However, it is stated that the liver extended only 4 cm. below the costal margin. The possibility of a carcinoma in the liver also must be considered.

DR. ALEXANDER: You are assuming that the patient had underlying cirrhosis?

DR. WADE: Yes. I think the original symptoms seven months prior to entry may have been due to cirrhosis.

DR. ALEXANDER: Subsequently, the patient developed evidence of significant liver dysfunction as indicated by results of the cephalin-cholesterol flocculation test, the high serum globulin and the decreased prothrombin time. The urine urobilinogen also rose.

DR. WADE: The increase in urine urobilinogen, I believe, indicates definite hepatic disease.

DR. GUSTAVE J. DAMMIN: I agree that the increasing urine urobilinogen suggests impairment of liver function.

DR. ALEXANDER: How may the distinction between cirrhosis and hepatitis in a situation such as this be made? The patient was jaundiced before his terminal illness; may a similar clinical picture arise in acute hepatitis?

DR. WADE: Yes, I think that it might. I prefer, however, to link all of the patient's symptoms in the course of the last seven

months together and that could be done better with a diagnosis of cirrhosis.

DR. ALEXANDER: On the other hand, as far as the clinical history goes, there was no continuity of symptoms. The patient had a brief episode and was then quite well for six months. Nevertheless, your point is well taken.

DR. WADE: The red count of 3,500,000 would be more compatible with cirrhosis than with uncomplicated acute hepatitis but in the presence of hematemesis the anemia cannot be used *per se* to support the diagnosis of cirrhosis.

DR. SCHEFF: I would like to ask Dr. Wade how frequently advanced cirrhosis is seen in a patient of this age.

DR. WADE: It is true that the incidence of cirrhosis increases with advancing age and is most marked in the fifth and sixth decades, but advanced cirrhosis may be seen in fairly young people and it is occasionally seen even in young children.

DR. WILLIAM H. OLMSTED: The size of the liver as described seems small for carcinoma.

DR. WADE: The liver need not be enlarged for carcinomatous change may be quite localized.

DR. ALEXANDER: In the presence of cirrhosis how frequently is the gallbladder normal?

DR. SCHEFF: In my experience gallbladder disease occurs quite frequently in patients with cirrhosis.

DR. ALEXANDER: Although the primary diagnosis remained a problem, the patient suddenly developed signs pointing to a change in the status of the abdominal lesion. His temperature and white count rose and the differential count shifted to the left. These changes occurred before the first paracentesis. There was a suggestion of air under the diaphragms and some indication of peritonitis. Dr. Kenamore, do you believe that rupture of a viscus occurred?

DR. KENAMORE: Yes, I do.

DR. PALMER H. FUTCHER: I am not sure that I agree that either rupture of a viscus or peritonitis existed. The coliform organisms conceivably could have been contaminants. I believe thrombosis of the portal vein must be considered, for it can produce symptoms very similar to those observed in this case.

DR. ALEXANDER: If there was peritonitis due to a coliform organism, might the organisms themselves form enough gas to be visible roentgenologically?

DR. CARL G. HARFORD: I do not think so.

DR. SAMUEL C. BUKANTZ: The patient's acute episode with pain developed before the first paracentesis and the air under the diaphragm was noted after the paracentesis. How often may air be seen under the diaphragm following paracentesis?

DR. ALEXANDER: Your point is a good one for paracentesis may lead to air under the diaphragm frequently. However, the presence of coliform organisms suggests the likelihood of peritonitis which certainly may have arisen as a result of perforation.

DR. OLMSTED: I believe that pancreatitis should be mentioned.

DR. ALEXANDER: Yes, pancreatitis could have explained the pain and it is true that the serum amylase rose. It was suggested earlier that the patient may have had an ulcer of the duodenum which ruptured into the pancreas giving rise to pancreatitis with the associated high amylase.

DR. DUDEN: I should like to mention a case recently seen in which marked constriction of the duodenum seemed apparent from roentgenologic studies. A diagnosis of annular pancreas was made and the patient was explored. At operation no cause for the narrowing was found. It must be emphasized that narrowing such as was seen here may occur without extrinsic pressure.

DR. ALEXANDER: It is apparent that no general agreement can be reached on the

primary diagnosis or the cause of death in this case. Considerable opinion favors cirrhosis of the liver. It is possible that the patient had a duodenal ulcer with rupture either into the peritoneal cavity or into the pancreas; if the latter occurred, pancreatitis resulted. It seems likely that the patient had peritonitis due to a coliform organism, but it is possible that the terminal abdominal symptoms were due to thrombosis of the portal vein and that the air under the diaphragm arose as a result of the paracentesis.

Clinical Diagnosis: ?Laennec's cirrhosis; ?duodenal ulcer with rupture into the peritoneal cavity or the pancreas with resultant pancreatitis; peritonitis due to coliform organisms.

PATHOLOGIC DISCUSSION

DR. BETTY B. GEREN: At autopsy the body was that of a well developed, well nourished Negro male. The sclerae were markedly icteric and there was generalized enlargement of the superficial lymph nodes. On opening the thorax, petechiae and focal hemorrhages were found beneath the pleurae of the lungs and there was massive atelectasis of the lower lobes of both lungs and focal atelectasis of the other lobes. In the right pleural cavity there were 200 cc. of yellowish, blood-tinged fluid and 150 cc. of similar fluid were present in the left pleural cavity. Aside from petechiae beneath the epicardium, the heart was not remarkable. When the abdomen was opened, large numbers of gas bubbles were seen and the peritoneal cavity contained 4,500 cc. of bile-stained fluid. The liver weighed 1,100 Gm.; its surface was finely nodular, the nodules being yellowish and averaging 3 to 6 mm. in diameter. They were elevated 1 to 2 mm. above the intervening, firm, pinkish, fibrous tissue. The capsule was slightly thickened. On section similar yellowish nodules were seen, in marked contrast to

the firm, retracted, pinkish tissue in the widened portal spaces. Greenish pigmentation was seen in some of the portal spaces. The spleen weighed 160 Gm. and was markedly congested. In the esophagus, 11 cm. proximal to the cardia, there was a 1.5 by 1.0 cm. erosion of the mucosa but no varices were found. At the level of the cardia a 3.5 by 1.5 by 1.0 cm. irregular, firm, white tumor mass was present in the submucosa. The rugae of the stomach were markedly prominent and there was a large amount of mucus on the surface of the gastric mucosa. In addition, a small amount of granular material was present in the lumen and there were petechiae and focal hemorrhages in the mucosa of the fundus of the stomach. On the serosal surface of the first portion of the duodenum, 1 cm. distal to the pylorus, there was a 4 mm. perforation of the anterior wall. The ulceration involved all layers of the wall of the duodenum and measured 1.0 by 0.5 cm. on the mucosal surface. On the posterior wall of the duodenum there was an ulceration of the mucosa and submucosa, measuring 6 mm. in greatest diameter, which did not involve the muscularis or deeper layers. All of the peritoneal surfaces were covered with a yellowish-white exudate.

DR. MOORE: It is apparent that this patient had two major diseases. First, he had two duodenal ulcers in the first portion of the duodenum, 1 cm. and $\frac{1}{2}$ cm. from the pylorus, respectively, the closer one of which, lying anteriorly, had perforated through the entire thickness of the duodenum into the free peritoneal cavity. The ulcer on the posterior surface was superficial and extended only through the submucosa. Although headed in that direction, it had not reached the pancreas, and there was no evidence of pathologic change in that organ immediately below the ulcer. Second, the patient had cirrhosis of the liver of moderately advanced degree associated with slight

to moderate portal hypertension as evidenced by ascites. At autopsy there was no evidence, however, of chronic passive congestion of the portal system. The spleen weighed only 160 Gm., and although it was congested, the congestion may have been associated with the peritonitis rather than with long standing portal hypertension. The gastrointestinal mucosa did not show the degree of chronic passive congestion that would have been expected if cirrhosis of the liver had been responsible for marked portal hypertension. There were no pathologic changes in the gallbladder to account for the fact that it was not visible when cholecystography was performed. Dr. Duden's statement that the second portion of the duodenum may show apparent extrinsic pressure when no lesion involving that area could be found is borne out by the fact that in this case, no pathologic process involving the second part of the duodenum could be identified.

The microscopic sections are interesting in regard to the duration and nature of the lesions involving the duodenum and the liver. The first section (Fig. 1) is a striking example of a perforated ulcer at the point of perforation. It shows the mucosa of the duodenum on both sides, the base of the ulcer with the overhanging edge of slightly hyperplastic mucosa and the defect in the wall. The lower half of the slide represents the free peritoneal cavity. If one examines the tissue carefully, evidence of the age of the ulcer may be obtained. Figure 2 is from the peritoneal surface of the ulcer bed and shows the muscularis and the peritoneum. The latter is thickened by proliferation of connective tissue which is moderately mature. It still contains a goodly number of capillary vessels but the thickening is significant. Such changes cannot occur in less than weeks or possibly months. It is seen that the base of the ulcer is completely devoid of muscular tissue. No necrosis is

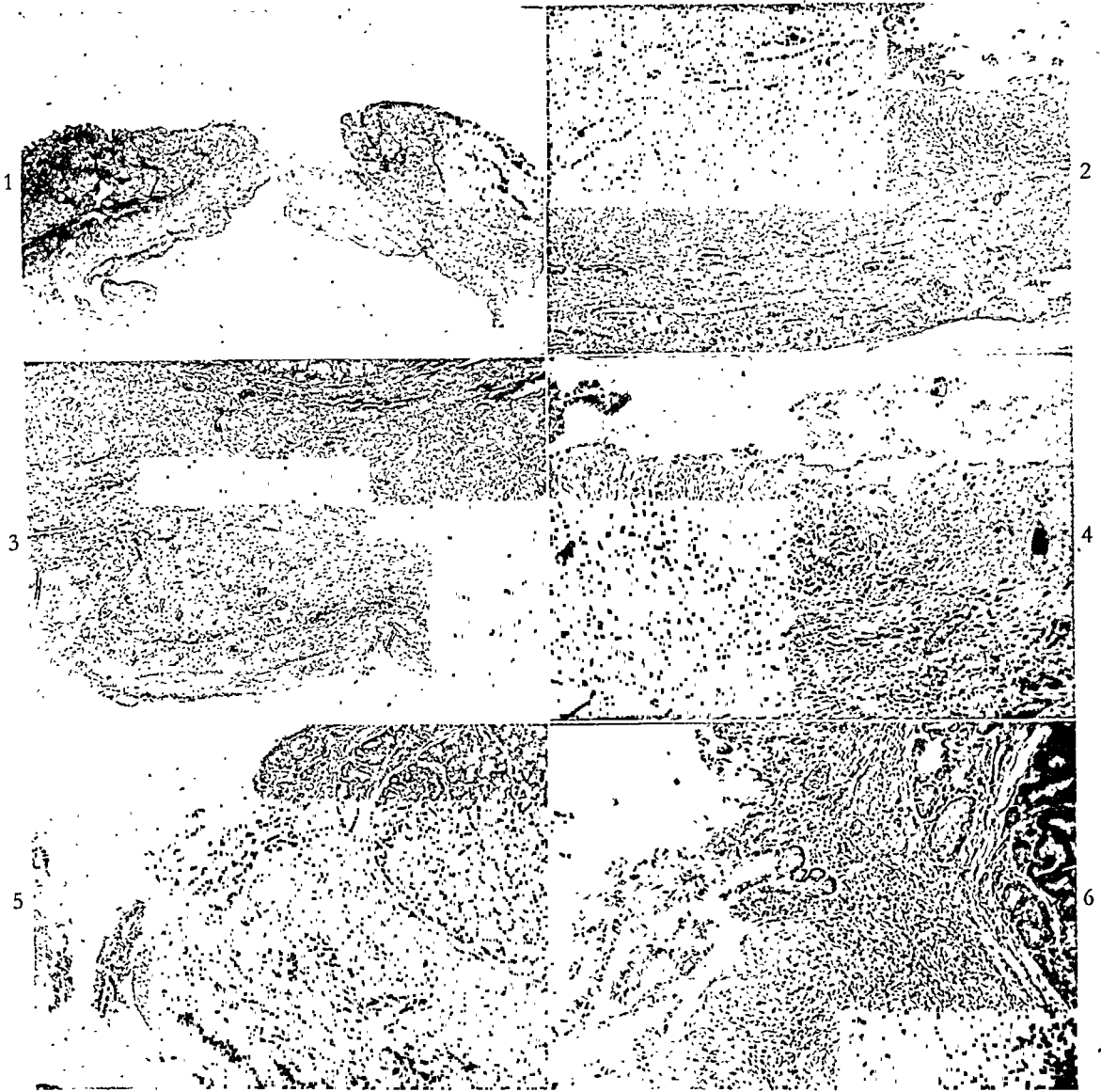


FIG. 1. Low power photomicrograph at the site of the perforated ulcer.

FIG. 2. Section showing the peritoneal surface of the ulcer bed in the region of the perforation.

FIG. 3. Section of the peritoneum showing changes indicating a chronic ulcer.

FIG. 4. Section through the bed of the ulcer showing layers of necrosis, granulation tissue and collagen.

FIG. 5. Section at the edge of the ulcer with epithelium on its surface.

FIG. 6. High power view of Figure 5.

evident in the muscle at the point of perforation, again indicating that the perforation occurred some time before death. In other words, there was an attempt at repair which is seen in a chronic or subacute peptic ulcer. Figure 3 shows the peritoneum in another area. There is again great thickening, indicative of chronicity as far as the

ulcer is concerned. In Figure 4 the bed of the ulcer is seen with the characteristic three layers previously described, namely, the superficial layer of necrosis, a layer of granulation tissue and far beneath a layer of collagen in which the granulation tissue has undergone maturation. The formation of collagenous granulation tissue is another

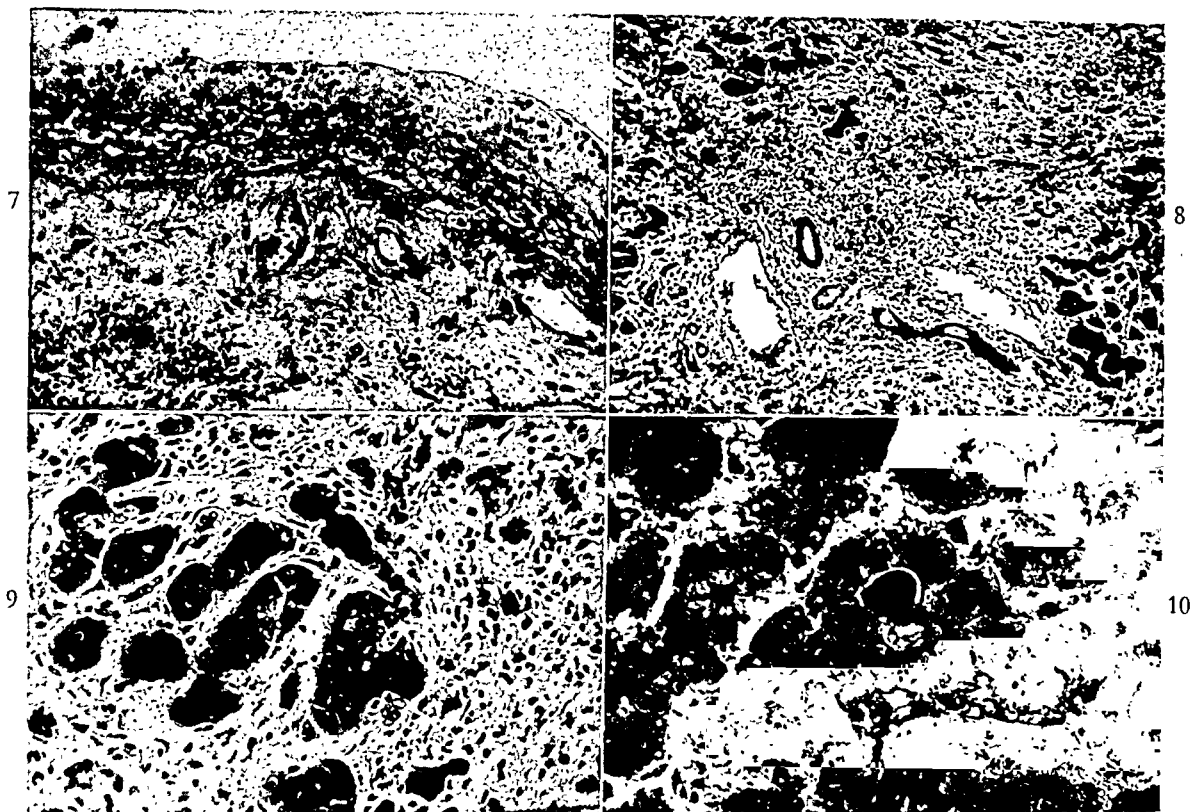


FIG. 7. Section showing the changes of peritonitis.

FIG. 8. Section of the liver illustrating the process of cirrhosis.

FIG. 9. Section from the liver showing two columns of liver cells separated by a bile duct.

FIG. 10. Another section from the liver, under higher magnification, showing intrahepatic obstruction with distention of bile canaliculi.

indication of chronicity of an ulcer. The thick layer of necrotic tissue also indicates activity. Further evidence in regard to the age of the ulcer is seen in Figure 5, showing epithelium on the surface of the edge of the ulcer which may have been desquamated from that surface. If the surface was covered by epithelium, it was a healing peptic ulcer and suggests that the patient may have had a period of activity following which there was healing and then, a week or so before death, new activity and a new erosion occurred. Figure 6 shows a higher power view of the edge of the ulcer with the single layered epithelium which may have been desquamated from the edge. I believe that it was most probable that the ulcer was healing and that activity occurred shortly before death and led to perforation. In Figure 7 the peritonitis is seen. There is a

fibrinoseous and slightly cellular exudate indicating an acute lesion.

Considering the liver, in Figure 8 a portal space is seen showing recent connective tissue, cellular infiltration and isolation of individual liver cells throughout the connective tissue. This process indicates fairly active cirrhosis of the type in which there has been widespread destruction of the liver and regeneration of both lobules as well as of individual groups of liver cells out in the connective tissue. It is the type of change that twenty years ago would have been called "toxic cirrhosis of the liver"; today, we are not clear as to the exact origin of the process, for it may come from a number of initiating lesions.

In regard to the problem of where regenerating liver cells arise, that is, whether from other liver cells or from bile ducts, it is

of interest to examine Figure 9. A small bile duct is seen between two columns of liver cells. This finding might be interpreted as indicating that the liver cells are actually arising from the bile duct but such an interpretation is only a postulation and not a statement of proven fact.

Figure 10 shows the reason for the patient's jaundice. There is intrahepatic obstruction and the intercellular bile canaliculi are distended with bile and in certain areas, so-called bile thrombi have been formed by dilatation of the intercellular bile canaliculi.

Summarizing then, it can be said that the patient probably had a peptic ulcer for some time, possibly healing until a short time before death when it became reactivated leading to perforation and peritonitis. There was also active cirrhosis of the liver, possibly toxic in type. Since in the clinical discussion Dr. Alexander brought up the question of infectious hepatitis, it will be of interest to present three current views concerning the relation of infectious hepatitis to cirrhosis of the liver. I shall quote significant statements from each of three important papers recently published. First of all, a paper by Balduin Lucké,¹ summarizing the Army material: "In the present investigation there was found no evidence of permanent damage to the hepatic parenchyma and restora-

¹ LUCKÉ, B. Structure of liver after recovery from epidemic hepatitis. *Am. J. Path.*, 20: 595-619, 1944.

tion of the liver was practically complete." The next selection is from the experience of Dible² in England: "That acute and subacute necrosis and cirrhosis could follow epidemic hepatitis has been recognized previously. Our studies further emphasize this sequence." Wood,³ reporting the work in the United States Navy, said: "There is lack of agreement among pathologists as to whether or not cirrhosis may result and if it does, whether it is of the so-called toxic or portal type." Whether or not this man had epidemic hepatitis as a forerunner of his cirrhosis, I do not know.

DR. ALEXANDER: The esophageal lesion was of no significance?

DR. MOORE: It was a leiomyoma and clinically insignificant. The esophageal ulcer was a terminal one in a person who had vomited a great deal.

Pathologic Diagnosis: Subacute and chronic peptic ulcers of the duodenum with perforation of one; serofibrinous peritonitis, generalized (4,500 cc. bile stained fluids and large amounts of gas in peritoneal cavity; *Escherichia coli* cultured from ascitic fluid and blood stream at autopsy); atelectasis of the lungs, massive of the lower lobes, and focal of the nodular cirrhosis, advanced.

² DIBLE, J. H., McMICHAEL, J. and SHERLOCK, S. P. V. Pathology of acute hepatitis; aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet*, 2: 402-408, 1943.

³ WOOD, DAVID. Further notes on the pathology of acute epidemic hepatitis and hemologous serum jaundice. *Am. J. Clin. Path.*, 16: 746-751, 1946.

False Positive Biologic Tests in Lymphogranuloma Venereum*

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As a result of the advances in the separation of human blood protein into several fractions,¹ an increasing number of biological phenomena are being attributed to the globulin components of plasma. Fractions in the normal globulin partition or in hyperglobulinemia appear to be responsible factors in a number of laboratory tests which have not previously been well understood. These include the Wassermann reaction,² cephalin-cholesterol flocculation and colloidal gold tests,^{3,4} Takata-Ara reaction⁵ and formol gel test.

Lymphogranuloma venereum is a disease in which hyperglobulinemia is a common finding.^{5,6,7,8,9,10,23} Though Mann¹⁰ reports this to be particularly true of the chronic phase of the disease in which the globulin may be permanently elevated, Kampmeier, Smith and Larsen⁹ report its presence in sixty-two out of sixty-seven patients in early stages. In a series of seventy-nine patients Jones and Rome⁵ found the globulin concentration to be greater than 3 Gm. per cent in 95 per cent, with significant and rapid variations occurring over a short period of time. One might expect therefore in this disease a high incidence of false positive laboratory tests which are attributed to a high globulin concentration. Clinical reports of such phenomena are surprisingly few and those which do exist are largely concerned with false positive serologic and anticomplementary Wassermann reactions. Jeghers

and Selesnick¹¹ found that hyperproteinemia especially in lymphogranuloma venereum and multiple myeloma gives rise to anticomplementary Wassermann reactions. Stokes¹² and others report the anticomplementary reaction as being common in lymphogranuloma. Johnson and Burnet⁷ state false positive serologies are found in 5 to 10 per cent of cases of lymphogranuloma while Koteen¹³ states the incidence is as high as 33 per cent. The true incidence of these reactions is difficult to ascertain largely because of the transitory nature of the Wassermann reaction. Jones and Rome⁵ reported a high incidence of positive Takata-Ara reactions in ninety-nine cases of lymphogranuloma venereum. Of this number, fifty had positive reactions with no evidence of disturbance in liver function as indicated by the bromsulfalein, the urine urobilinogen, the van den Bergh and the galactose tolerance tests. Forty-seven of the fifty cases had associated elevation in globulin.

It is rare that one has the opportunity to study lymphogranuloma venereum in the early stages, which may explain the variable clinical reports on false laboratory tests. The following case is therefore reported.

CASE REPORT

L. L. was a forty-three year old male Negro who was admitted to the Presbyterian Hospital with a painful swelling in the left groin of three weeks' duration. The patient acknowledged

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LABORATORY DATA

Date	E.S.R.*	Total Serum Protein†	Serum Globulin†	Cephalin Flocculation	Heterophile Agglutination	Serology	Miscellaneous
1-5-45		7.2	3.2			Kline 0 Wassermann 0	
1-8-45	80						Temperature 105.4°F. WBC 12,650
1-9-45		7.9	4.4	+++		Kline 0	Cold agglutination 1:32
1-11-45	93				1:128		WBC 6,900
1-12-45							Temperature normal
1-15-45	108			+++		Kline 0 Wassermann Alcohol lic +++++ Cholesterol +++++	
1-16-45		7.7	4.3				WBC 9,850
1-19-45	62						Frei test ++
1-21-45		Discharged					Frei test (autoantigen) ++
1-30-45	27	7.7	3.2	+	1:32	Kline 0 Wassermann 0	Cold agglutination 0
2-6-45	14	7.5	3.0	0	1:16		
2-20-45					1:32		

* Sedimentation rate in mm/hr. Normal maximum 15 mm.

† Values given in Gm. per cent.

having had sexual intercourse four weeks before the onset of his first symptoms. Though he did not notice a herpetic penile sore, his symptoms of low backache began four weeks prior to admission. Three weeks prior to admission he developed a small, painful, marble-sized lump in his left groin which slowly increased to the size of a walnut and one week prior to admission he developed headache, chills, fever and malaise. Upon admission he had a temperature of 105°F. (p.r.) but because of its subsequent subsidence to 99.8°F. (p.r.) in forty-eight hours he was allowed to return home. Two days later he returned to the hospital with the same symptoms.

The patient's temperature was 105.4°F. (p.r.), pulse 100, blood pressure 122/72.

On second admission to the hospital the patient was an acutely ill but well developed and well nourished Negro male. His sclerae and conjunctivae were injected and there was a loud blowing systolic murmur heard in the mitral area. In the left groin there was a fusiform swelling 2 by 5 cm. with no heat and redness but deeply fluctuant and somewhat tender.

The above laboratory data in tabular form indicate the changes that occurred in the patient's hospital course. Additional data not included are: negative bubo pus and blood

cultures, hemoglobin 13.6 Gm., red blood count 4.70 million. Repeated blood smears were negative for infectious mononucleosis cells.

The patient was given sulfathiazole in the dose of 2 Gm. initially and 1 Gm. every six hours. With drug levels of 3 mg. per cent there was a dramatic drop in temperature and a marked disappearance of the constitutional symptoms within forty-eight hours.

The patient was discharged on the thirteenth hospital day on a maintenance dose of sulfathiazole of ½ Gm. three times daily. He was followed in the out-patient department weekly for one month. Two weeks after discharge chemotherapy was discontinued and the patient remained asymptomatic. At the time of the last clinic visit the laboratory data had reverted to normal.

COMMENT

The clinical response to chemotherapy would appear to be more dramatic than what one would normally expect. Noojin et al.,¹⁴ however, reported ten cases of lymphogranuloma venereum treated with either sulfathiazole or sulfadiazine, with all patients afebrile in twenty-four hours. The

dose used was larger than that employed here, i.e., 6 Gm. the first day and 3 Gm. daily for twenty days.

In addition to the laboratory data recorded, attempts were made to prove the existence of the lymphogranuloma virus in bubo pus by animal transmission experiments and the preparation of an antigen.

Bubo pus was aspirated on the second hospital day. This cultured negative, and on smear contained a predominance of mononuclear cells. An antigen was prepared after the method first described by Frei¹⁵ in 1925 in which the bubo pus is diluted five times with normal saline, and sterilized by heating to 60°C. two hours the first day and one hour the second day. The material is tested for sterility and stored in a refrigerator.

This antigen was employed as skin test material not only on this patient but on other known Frei-positive individuals. In four patients known to have positive Frei tests* and one with the clinical manifestations of lymphogranuloma venereum, this antigen produced a positive skin test in every case. In four known normal Frei-negative patients* this preparation gave a negative reaction.

An attempt was made to transmit the viral agent in the bubo pus to yolk sacs of the chick embryo and mouse brain. Injection of the bubo material into the yolk sacs of chicken embryo produced no growth. Several white mice were injected intracerebrally with diluted bubo material. None of the animals developed characteristic signs of cerebral involvement (humped back, ruffled hair, tremors, ataxia, paralysis and convulsions). However, the use of sulfathiazole previous to aspiration of the bubo may have sufficiently reduced the virulence of the virus. Callomon and Brown¹⁶ found the virus present in the brains of mice injected intracerebrally and treated with sulfonamides. Though the

animals did not show any clinical evidence of infection, pathological material showed characteristic cellular changes in the brain substance.

In the case reported a significant increase in globulin concentration was noted during the active virus infection. This increase occurred over a relatively short period of time and it was during this period that four serological tests became positive, a phenomenon more commonly associated with other infections. It is doubtful whether this can be attributed solely to an increase in globulin, and therefore altered globulin (s) is suggested as the basis for some of these reactions. These four serological tests are discussed below.

The cephalin-cholesterol flocculation test is closely related to disturbances in the protein partition.²² Hanger et al.^{3,4} have demonstrated that gamma globulin is the sole component of serum protein giving a positive cephalin flocculation and that a positive reaction can be expected when an increase in gamma globulin is not sufficiently inhibited by serum albumin. In the case reported the return of the cephalin flocculation to normal from three plus was coincident with the return of elevated globulin to a normal range.

Cold agglutination is considered by most workers to be a non-specific response to infection. Though this phenomenon occurs most commonly in primary atypical pneumonia,^{17,18,19} it is present in a variety of other diseases,^{18,20} particularly those of viral origin. Cold agglutinins are probably present in the globulin fraction of plasma. A titer of 1:32 in this case was considered significant in that it returned to zero when the infection was no longer active.

The heterophilic antibody reaction is considered specific for infectious mononucleosis but increases in titer have been found in pneumonia, measles, tuberculosis, scarlet fever, filariasis, aplastic anemia and

* Previously tested with commercial yolk sac antigen.

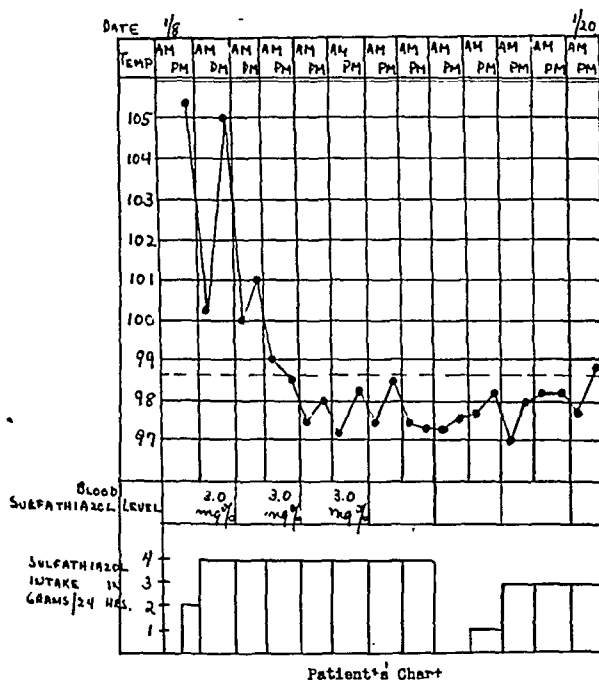


FIG. 1.

leukemia. Actually, the highest titers have been found in diseases other than infectious mononucleosis.²¹ The heterophilic antibody probably lies in the globulin fraction of plasma. Hyperglobulinemia does not appear to be associated with the Paul-Bunnell reaction and so the reversion of a titer of 1:128 to a normal range of 1:32 in this case should be attributed to the disappearance of the antibody as the infection became inactive.

Hyperglobulinemia is associated with anticomplementary Wassermann reactions while the true Wassermann reaction is due to a specific antibody. By electrophoretic studies² the Wassermann antibody has been found in the globulin fraction between beta and gamma globulins. There appears to be no difference between false positive and true positive Wassermann sera. An altered globulin presumably caused the transitory positive Wassermann recorded in the case reported.

Evidence indicates that these four serological tests (cold agglutination, cephalin flocculation, Wassermann reaction and

heterophile agglutination) lack specificity and that the basis for them is a disturbance in the globulin fraction. The table given below illustrates this non-specificity by demonstrating the frequent occurrence of positive results with these biological tests in four common virus diseases.

Disease	Cold Agglutination	Cephalin Flocculation	Wassermann Reaction	Heterophile Agglutination
Infectious mononucleosis.....	+	+++	++	+++
Primary atypical pneumonia..	+++	+	++	+
Lymphogranuloma venereum	+	+	+	+
Infectious hepatitis.....		+++	+	

+ reported in the literature

++ common

+++ very common

SUMMARY

1. A case of lymphogranuloma venereum is reported in which a number of falsely positive laboratory tests were found.

2. Cold agglutination, Wassermann reaction, cephalin-cholesterol flocculation, and heterophilic antibody reactions are discussed from the standpoint of non-specificity.

3. The evidence supporting the view that hyperglobulinemia with abnormal globulins forms the basis for many biological tests is presented.

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Juvenile Diabetes as a Sequel to Mumps^{*}

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IN a recent review of the literature it was noted that the usual complications of mumps cited were orchitis, nephritis, encephalitis and more recently, myocarditis.¹ However, there was no mention made of diabetes mellitus as a sequel of this disease. Pancreatitis was mentioned as a complication of mumps, and this was associated with the familiar symptoms of acute abdominal pain, vomiting, and a picture of acute abdominal catastrophe, but there was no reference to any patients with an acute onset of hyperglycemia or glycosuria.

The occurrence in two patients of diabetes in which mumps appeared to play a part in the etiology would therefore seem to merit consideration.

CASE REPORTS

CASE I. The patient was a fifteen year old white male who six weeks before his admission to the hospital was ill with the mumps and was confined to bed for three weeks. He then noted nocturia and frequency. He drank a great deal of soda during the day and had an increased appetite for food. He had lost weight since the onset of his illness.

He had a past medical history of measles, pertussis and varicella. Tonsillectomy had been performed in July, 1945. The family history was negative for diabetes. The physical examination was negative. The fasting blood sugar was 165 mg. per cent. Urinalysis showed sugar, four plus. The patient was put on a diet of P-80, F-80 and CHO-135. The insulin dosage was determined at 10P-0-10P. The blood sugar on discharge was 85 mg. per cent and the urine was free of sugar.

CASE II. The patient was an eleven year old white male who was first admitted to the hospital in November, 1942, because of polydipsia and polyuria. One month before admission the patient began to drink a great deal of water and to pass more urine. He also had had a cold for the past month.

The past medical history included pneumonia, tonsillectomy and whooping cough. He had had mumps about six weeks before admission. Physical examination was negative. The urinalysis revealed sugar four plus, and the blood sugar was 200 mg. per cent. He was standardized at the hospital and was put on a diet of P-75, F-100 and CHO-125. The insulin dosage was 15P-0-10P. On November 18, 1942, the patient had a slight insulin shock and the insulin was reduced to 15P-0-10P from 20P-0-15P. He remained so standardized and continued to do well until June 28, 1943, when he was admitted to the hospital with scarlet fever. He ran a blood sugar of 68-296 mg. per cent. He went to the seashore to convalesce and his weight increased from 73 to 78 pounds. The blood sugar in September, 1943, was 150 and he was given 15P plus 5-0-10. In November, 1943, the blood sugar was 350 mg. per cent and the urine sugar was four plus. Insulin dosage was 15-P-10-10P. In December, 1943, the insulin was 20P plus 5-0-10. In January, 1944, the sugar in his urine was negative for three days, and the blood sugar was 180. The insulin was then 20P plus 5-0-10P. He continued to gain weight. In June, 1944, the blood sugar was 235 mg. per cent two hours after breakfast. He had an episode of acidosis on July 28, 1944, and he was given 30P-7-0-5. By the end of 1944, he weighed 96 $\frac{3}{4}$ pounds. In October, 1945, he had an attack of gastroenteritis which upset his regulation. His weight in June, 1946, was 108 pounds and the blood sugar was 380. Insulin

^{*} From The Doctors' Hospital of Philadelphia, Philadelphia, Pa.

dose was set at 30P plus 10-0-10 and the patient has been faring well ever since then.

COMMENT

The chronologic sequence of events in the two reported case histories permits us to surmise that there may have been a causal relationship between the occurrence of mumps and the onset of overt diabetes mellitus. The four-year course in the second patient certainly suggested that the condition had become well established. Interestingly enough, as in most juvenile diabetics, the management of the patient was difficult as indicated by the frequent change in the insulin regimen.

CONCLUSIONS

Two patients with diabetes mellitus in whom epidemic parotitis probably was a causative factor have been presented. No symptoms of diabetes antedated the attack of mumps in either case. Unfortunately no data are available as to glycosuria or hyperglycemia before or during the course of mumps; however, the clinical course following mumps suggests that this virus disease might have been a causative factor, possibly as the result of concomitant involvement of the pancreas.

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Editorial

Late Results in Peptic Ulcer

PEPTIC ulcer, whether gastric or duodenal, has a natural tendency to heal. In some instances this occurs without any medical supervision, and usually, when the lesion is of recent origin and uncomplicated, the symptoms can promptly be brought under control by the frequent feeding of a non-irritating and nutritionally adequate diet together with the avoidance of undue physical and nervous strain. Recurrence of activity, often with complications, is common, however, irrespective of the degree of gastric acidity and of whether additional therapeutic procedures, such as bed rest, antacid medication, sedation and even psychiatric measures, were originally employed. Apparently this results from some poorly understood predisposition on the part of the patient and the fact that, because of the relatively long intervals of freedom from symptoms, he tends to revert to his customary life habits.

A review of the current literature on the ultimate results in this disease is discouraging. It indicates that less than half of the roentgenologically diagnosed peptic ulcer patients are permanently cured on a medical basis. Of 216 such patients followed for ten years, Holland and Logan¹ found only 38 per cent without a recurrence and, in 1938, Crohn² reported only 27 per cent of

this patients cured after four years. Nicol³ had good results in only 38.5 per cent of 278 patients after two to twelve years, and some of them had symptoms when indiscreet about their diet. Raimondi and Collen⁴ had an 83 per cent incidence of recurrence in patients treated for two years, and St. John and Flood⁵ only 22 per cent free of recurrence after five years. Only Eustermann and Balfour⁶ give more encouraging results: 65 per cent of 600 duodenal ulcer patients cured or relieved after three to five years.

In a recent report⁷ on 923 patients followed from one to ten years at the University of Pennsylvania Hospital, most of them treated originally on an ambulatory basis, 31.5 per cent had come to operation within the first year of observation for a refractory status or some complication, other than malignancy, and an additional 14 per cent were still having symptoms irregularly; of the 444 patients followed for five years, 36

treatment and end results. *New England J. Med.*, 218: 128, 1938.

³ NICOL, B. N. Peptic ulceration: results of modern treatment. *Lancet*, 1: 466, 1942.

⁴ RAIMONDI, P. J. and COLLEN, M. F. Recurrent rate of symptoms in peptic ulcer patients on conservative medical treatment. *Gastroenterology*, 6: 176, 1946.

⁵ ST. JOHN, F. B. and FLOOD, C. A. Study of results of medical treatment of duodenal ulcer. *Ann. Surg.*, 110: 37, 1939.

⁶ EUSTERMANN, G. B. and BALFOUR, D. C. Stomach and Duodenum. Philadelphia, 1936, W. B. Saunders & Co.

⁷ MILLER, T. G. Results from the treatment of peptic ulcer. *J. Michigan M. Soc.*, 46: 198, 1947.

¹ HOLLAND, A. L. and LOGAN, V. W. Brief report of follow-up research in peptic ulcer covering 20 years. *Tr. Am. Therap. Soc.*, 41: 86, 1942.

² CROHN, B. B. Gastroduodenal ulcer: etiology,

per cent had been operated upon and another 11 per cent were medical failures; of the 166 followed for ten or more years, 45 per cent had been operated upon and an additional 10 per cent were not relieved. On the other hand, it is interesting to note that of the patients operated upon and followed for corresponding periods of time—one, five and ten or more years—the satisfactory results were about 80 per cent in each instance. Thus, although a medical regimen obviously failed in about half the cases, the total therapy, including surgery, led to symptomatic relief in approximately four of every five cases for each follow-up period. This consistent level of relief from symptoms for the varying periods of observation was accomplished, however, only by subjecting a steadily increasing percentage of the patients to surgical interference, from 31 per cent for the one-year

group to 45 per cent for the ten or more year group.

In view of these results a most important aspect of the management of the peptic ulcer patient is to acquaint him at the first opportunity with the marked tendency to a recurrence of activity and to serious complications, so that he may make every reasonable effort to maintain a dietary and hygienic program designed to avoid such developments. The fact that many ulcers heal spontaneously is probably dependent on the fact that the leading symptom is that of hunger, which naturally leads to the ingestion of food substances between regular meals. Such frequent feedings, provided they are of a non-irritating nature, constitute the chief therapeutic procedure in the prevention and cure of the disease.

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Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis^{*}

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TO understand the rationale of antibiotic aerosol therapy in certain types of pulmonary and bronchial suppurative disease, it should be remembered that the normal bronchial tree has both ventilatory and drainage functions. The bronchi and bronchioles lengthen and widen in inspiration, and shorten and narrow in expiration. Drainage is facilitated by these rhythmic contractions, by the normal ciliary action of the epithelium of the tracheobronchial tree, and by the expulsive force of the elastic recoil of the lungs and piston-action of the diaphragm in expiration.

The anatomical changes occurring in bronchiectasis are permanent. Actual destruction of bronchial musculature and elastic tissue may occur as a result of suppuration, accompanied by dilatation of the bronchial wall, which may be cylindrical or saccular in character. The bronchial epithelium in the involved region may change from ciliated columnar to cuboidal or squamous, with loss of the protective ciliary action. The site of commonest involvement is in the peripheral bronchioles. A certain amount of fibrosis of the bronchial wall occurs in the repair process as well as in peribronchial lung parenchyma, with or without associated emphysema.

In suppuration involving the pulmonary parenchyma, excavation may occur, with varying degrees of pneumonitis surrounding the lung abscess. If the abscess heals and closes, there is a residual fibrous scar. Bronchiectasis of the segmental bronchioles may be present. Even with complete x-ray clearing by stereoscopic films of the chest, a residual abscess cavity, or evidence of bronchiectasis, may be demonstrated by lipiodol instillation.

In both bronchiectasis and residual lung abscess, repeated respiratory infections cause exacerbation of the original disease. Local extension of the lesion may occur, or bronchogenic dissemination to other portions of the lung. Concomitantly, pulmonary fibrosis with secondary emphysema may develop, resulting in appreciable loss of pulmonary function and further stagnation of purulent material in involved areas.

Chronic bronchitis is uncommon as a separate disease entity. It is characterized by inflammation of the bronchial mucosa with hyperemia and edema, which may result in some areas of mucosal hypertrophy and others of atrophy. The bronchial walls and peribronchial tissue usually show fibrosis. Some dilatation of the bronchi may occur.

In cases in which a diagnosis of bronchiect-

^{*} From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York. This study was aided in part by a grant from the Josiah Macy, Jr. Foundation.

tasis, lung abscess or chronic bronchitis has been made, bronchoscopy is generally indicated to rule out obstruction in the tracheo-bronchial tree which would interfere with free drainage and ventilation.

The aim of medical management in these diseases is control of infection and prevention of further irreparable damage. If there is no obstruction, drainage of purulent exudates may be facilitated via the tracheo-bronchial tree either by postural drainage or by bronchoscopic aspiration. General hygienic measures and supportive therapy play a rôle. Use of oral sulfonamides has been disappointing on the whole except in control of some acute flare-ups when sputum cultures reveal the presence of sulfonamide-sensitive bacteria. Penicillin by intramuscular injection has been of considerable value. Surgery remains the treatment of choice in cases of bronchiectasis localized to a lobe or to lobes which may safely be extirpated. Many cases of chronic lung abscess require surgery, either drainage, lobectomy or pneumonectomy, for complete clinical cure. In considering cases of acute lung abscess and suppurative pneumonia, the advent of antibiotics has decreased the incidence of those requiring surgical intervention. Use of antibiotic therapy pre- and postoperatively has resulted in a decrease in postoperative complications and in operative mortality.

The purpose of antibiotic aerosol therapy is two-fold: first, local application of the drug to the diseased part; and second, systemic absorption of the drug via the pulmonary capillary bed.

HISTORY

The inhalation of nebulized solutions was extensively studied by Heubner (1919–1925),¹ who noted that the production of fine particles was necessary for penetration to the bronchioles and the alveoli. The beneficial clinical results of inhalation of an

aerosolized solution of 1:1000 epinephrine was correlated with an observed increase in vital capacity and velocity of breathing by Lageder.² Although many other drugs, such as glycerin, camphor and creosote, were tried in earlier investigations, bronchodilator substances were found most useful, especially 1:100 epinephrine with the hand bulb nebulizer proposed by Graeser and Rowe.³ Continuous nebulization with oxygen from a high pressure cylinder was employed in our clinic to nebulize 1:100 epinephrine and 1 per cent neosynephrine in the treatment of asthma and pulmonary emphysema^{4,5} and later for chemotherapeutic substances, such as promine⁶ and the sulfonamides.⁷

That nebulized solutions penetrated to the depths of the lungs was clearly confirmed by the careful studies of Castex, Capedehourat and Pedace⁸ as well as by Krueger et al.⁹ In a clinical study by Castex et al.¹⁰ inhalation of nebulized 5 per cent aqueous sulfanilamide was shown to be followed by marked clinical improvement in cases of bronchopulmonary suppuration. Clinical improvement following inhalation of nebulized sulfathiazole was reported by Stacey¹¹ and others whose observations have recently been reviewed by Segal.¹² In 1944, Bryson, Sansome and Laskin¹³ demonstrated that penicillin aerosol was absorbed in the lungs and excreted in the urine in substantial amounts in a normal human subject and in rabbits.

The clinical effectiveness of inhalation of penicillin aerosol by various technics in patients with bronchial asthma, bronchitis, bronchiectasis, lung abscess and pulmonary emphysema was described by Barach et al.^{14,15,16} This study indicated that the predominating gram-positive organisms in the sputum culture were absent following adequate penicillin aerosol therapy and that gram-negative organisms, such as *B. aerogenes*, *B. coli* and *B. pyocyaneus* appeared

in the sputum culture. An effective blood level was maintained in addition to the application topically of penicillin. Since that time, favorable reports on the inhalation of penicillin aerosol have appeared, notably by Segal^{17,18,19} in cases of bronchiectasis, lobar pneumonia and lung abscess; by Olsen^{20,21,22} in bronchiectasis; and by Vermilye²³ in bronchial asthma and various types of sino-bronchial infection. Anderson and di St. Agnese²⁴ showed that children with a staphylococcus bronchitis and pneumonitis which developed in association with pancreatic disease were markedly benefited at times by inhalation of penicillin aerosol when improvement had not been obtained previously by intramuscular injection of penicillin.

Interest in the inhalation of nebulized penicillin was promptly aroused in England where Mutch and Rewell²⁵ and Knott and Clark²⁶ carried out experimental studies on the production and absorption of aerosols, and clinical studies were made by Humphrey and Joules,²⁷ Southwell,²⁸ Knott and Southwell.²⁹ Studies on the methods and clinical application of penicillin aerosol have been continued in our clinic, especially in the development of a method for introducing the drug into the sinuses by previous intermittent production of negative pressure in the nasal passages.^{30,31,32}

METHODS

Various modifications have been made in the nebulizer apparatus as well as in techniques of inhalation since the earlier methods of aerosol therapy were reported. These modifications were intended to conserve penicillin, to give the highest possible local deposition of the drug, to insure maximum absorption into the blood stream, to increase the comfort and ease of inhalation and to decrease the incidence of local penicillin reactions manifested chiefly by a sore, reddened or blackened tongue.

Substitution of a 2.5 liter latex rebreathing bag for the enlarged glass bulb gives an adequate ventilation volume with less bulky apparatus. The lips are closed around the glass mouth attachment so that expired penicillin aerosol collects in the rebreathing bag and may be re-inhaled with freshly nebulized penicillin. A Y-tube inserted in the rubber pressure tubing between the oxygen regulator and the nebulizer allows nebulization of penicillin on inspiration only, since the patient closes the open end of the Y-tube with a finger at the start of inspiration and releases it at the end of inspiration, letting oxygen escape during the expiratory phase. Holding the breath for a second or two at the end of inspiration increases local deposition of the aerosol particles.

Oxygen is generally employed as the gas to nebulize the solution. Air from a pressure compressor may be used, or air supplied by means of an ordinary automobile tire foot-pump.³³ The latter has the advantage of being inexpensive and dispenses with the need for oxygen equipment in the home. If the patient is bedridden or too ill to work the pump himself, it can be operated by another person.

We have found the Vaponefrin nebulizer the most satisfactory of the various commercial nebulizers in regard to particle size of the aerosol. Investigators³⁴ reported that the majority of the particles are less than 1 micron in diameter. From studies under progress at the present time³⁵ a wider variation than was previously accepted has been found in particle size of aerosols produced by such nebulizers. Attempts are being made to determine the ideal diameter of particles for use as therapeutic aerosols, and thereafter to construct a nebulizer to produce as efficiently as possible an aerosol of such uniform particle size. Larger sized particles, such as those produced by some commercial nebulizers, tend to lodge on the



FIG. 1. Mouth inhalation apparatus with Vaponefrin nebulizer, curved glass baffle and mouth attachment with rebreathing bag immersed in hot water.

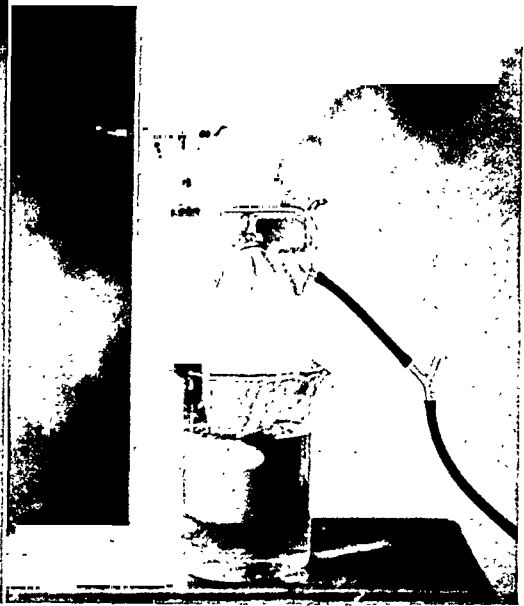


FIG. 2. Mouth inhalation apparatus with "small-particle-size" nebulizer connected to mouth attachment and rebreathing bag immersed in hot water.

tongue, pharynx and larynx and do not reach the bronchi, bronchioles or alveoli. Particles much smaller in size tend to be exhaled instead of deposited on the bronchopulmonary surface. By incorporation of a glass baffle between the Vaponefrin nebulizer and the mouth rebreathing attachment, the larger particles are baffled out and drain back into the nebulizer where the solution is renebulized. (Fig. 1.) A special nebulizer has been constructed which gives comparable results by producing an aerosol of finer particle size, with fair uniformity of particles and which eliminates the need for an additional glass baffle in the apparatus. (Fig. 2.)

Attachment of a metal water bottle to the oxygen regulator, although not an essential item, conserves penicillin by diminishing evaporation in the nebulizer. The oxygen flow employed varies from 8 to 12 liters per minute.

It has been found that comfort of inhalation is enhanced by providing a warm, humidified aerosol. This is accomplished

by placing a glassful of very hot water in the rebreathing bag immersed in a container of hot water. This modification also has decreased the incidence of local sensitivity reactions by surrounding the aerosol particles with water vapor. Patients who have previously shown a sore tongue reaction to penicillin aerosol are advised to rinse the mouth and gargle with tap water or warm saline following each treatment.*

Originally it was found that the calcium salt of penicillin was less irritating for aerosol use than the sodium salt. Since crystalline preparations have become available, they are the preparation of choice, in the form either of the crystalline sodium or

* More effective prevention of sore tongue is obtained by sipping water and rinsing the throat before and during inhalation of penicillin aerosol. Moistening the back of the throat by spraying with tap water, using a conventional atomizer, is probably the simplest and best method of avoiding irritation of the throat. This should be done before and during inhalation. The large particles that lodge on the pharynx are then taken up into solution on the moistened surface and subsequently absorbed. If this procedure is carried out, it is unnecessary to use hot water in the rebreathing bag.

potassium salt. It should be kept in mind, however, that this material, although the purest available, still contains some impurities, and some instances of sensitivity have been encountered even with its use.

The concentration of penicillin generally employed by us has been 50,000 units dissolved in 1 cc. of physiological saline. This gives a slightly hypertonic solution, whereas distilled water as the diluent gives a hypotonic solution. To obtain an isotonic solution using crystalline sodium penicillin, Wilson³⁵ found that 0.35 per cent saline would be required.*

The total daily dosage of penicillin aerosol recommended in treatment of bronchiectasis, lung abscess or chronic bronchitis varies between 150,000 and 500,000 units, generally divided into three to five inhalations, with a concentration of 50,000 units per cc. In a few cases, 1,000,000 units daily have been nebulized. At least one, and preferably two rinses of 0.5 cc. each of physiological saline are added to the nebulizer at the end of each treatment and inhaled to avoid waste of the drug from concentrated residue in the nebulizer. The time required for such a treatment, using the mouth inhalation apparatus, averages thirty minutes with an oxygen flow of 10 liters per minute.

In the treatment of patients too ill to use the standard mouth inhalation apparatus, in young children, and in most cases complicated by severe pulmonary emphysema, aerosols may be administered by a nebulizer attached to an oro-nasal mask (with the inspiratory disc removed) connected di-

* An aerosol tablet is now employed which eliminates the need for a hypodermic syringe and needle to make the solution used in nebulized penicillin therapy. The tablet contains crystalline penicillin, 50,000 units, and is inserted directly into the nebulizer; 8 to 15 minim drops of distilled or boiled water or saline are then added resulting in almost immediate solution of the crystalline penicillin tablet which is then nebulized. The crystalline penicillin tablets which we have employed were provided us by the Premo Pharmaceutical Laboratories, Inc., Commercial Solvents Corp. and the Bristol Laboratories.

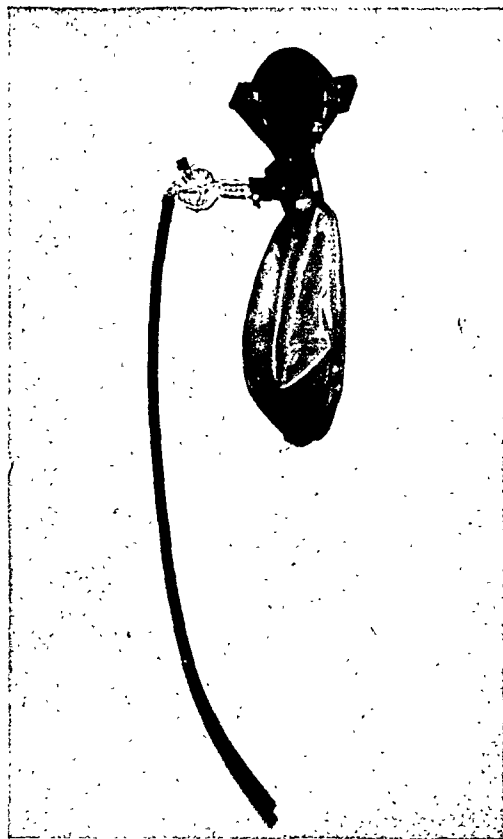


FIG. 3. Mask-nebulizer apparatus.

rectly by pressure tubing to the oxygen regulator without use of the concentration meter. (Fig. 3.) Whenever the inspiratory disc is removed the oxygen flow should be set at 8 liters per minute or higher to insure washing out of accumulated carbon dioxide from the rebreathing bag.

More recently we have become interested in methods of more continuous administration of penicillin aerosol. This may be accomplished by using the mask-nebulizer apparatus with a needle inserted through the cork of the carburetor opening in the nebulizer. The needle is then connected by infusion tubing to a large syringe or flask containing penicillin in a concentration of 5,000 to 10,000 units per cc. of saline. By use of a screw clamp on the infusion tubing, the rate of drip and consequent nebulization of solution is controlled.

A more comfortable method of continu-

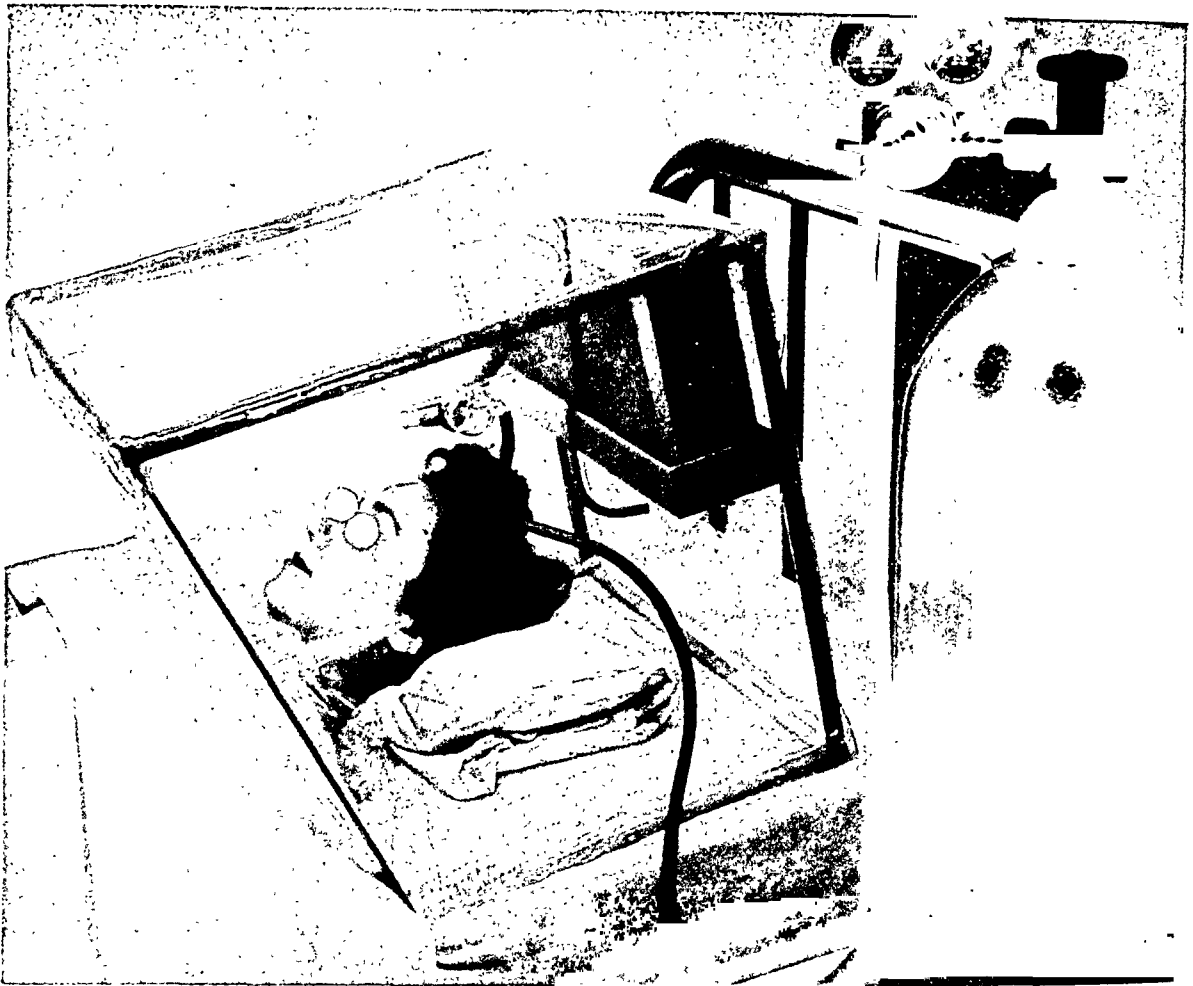


FIG. 4. Oxygen head tent for administration of continuous aerosol therapy.

ous aerosol administration is obtained by use of a clearlite oxygen head tent,³⁶ inside which the nebulizer is set in position so that a dense aerosol is directed towards the patient's nose and mouth. (Fig. 4.) The connection from the carburetor opening to the infusion flask is the same as for the mask-nebulizer apparatus. In the latter, 95 per cent oxygen is employed, whereas in the head tent technic an oxygen concentration of 50 to 60 per cent is obtained. By adjusting the concentration of penicillin and the rate of flow, this technic enables the patient comfortably to inhale penicillin aerosol for three to four hours at a time two to three times daily, or even continuously through the twenty-four-hour period, with only brief interruptions at meal times. The total

daily dosage generally varies from 500,000 to 1,000,000 units.

Efficient treatment by aerosol therapy of the bronchopulmonary diseases under consideration necessitates local deposition of the aerosol, which can be obtained only if the bronchial passageway remains open. Therefore, if much bronchospasm or congestion of the bronchial mucosa exists it is necessary to have the patient inhale a nebulized solution of Vaponefrin and 1 per cent neosynephrine prior to each inhalation of the antibiotic substance. Substitution of helium-oxygen mixtures may be employed in cases in which it is believed that the lighter gas will penetrate into diseased areas not accessible to oxygen.

RESULTS

The results of blood level determinations in patients given test inhalations of 50,000 units of penicillin dissolved in 1 cc. normal saline are shown in Table 1.* Two or three rinses of 0.5 cc. normal saline were added

reached and prolonging the blood level. It prevents too high concentration of penicillin in the nebulizer towards the end of inhalation by decreasing evaporation. This is important in patients prone to develop sore tongue reactions. We have found that the

TABLE 1
BLOOD LEVEL DETERMINATIONS AFTER INHALATION OF 50,000 UNITS PENICILLIN

Method of Inhalation	No. of Tests	Penicillin	Duration of Inhalation (Minutes)	Blood Levels (U/cc)		
				½ Hour	1 Hour	2 Hours
Cold dry aerosol	81	Calcium	35 (25-55)	0.10 (0.0-0.2)	0.07 (0.0-0.2)	0.03 (0.0-0.05)
Cold dry aerosol and water bottle	10	Calcium	60 (45-105)	0.07 (0.01-0.2)	0.13 (0.03-0.4)	0.08 (±0.2)
Warm humidified aerosol	17	Calcium	30 (20-70)	0.09 (0.0-0.2)	0.09 (±0.2)	0.04 (0.0-0.1)
Warm humidified aerosol and water bottle	20	Calcium	55 (40-90)	0.12 (0.05-0.2)	0.13 (0.05-0.2)	0.07 (0.01-0.2)
Cold dry aerosol	12	Sodium, crystalline	25 (10-40)	0.13 (0.0-0.4)	0.12 (0.05-0.2)	0.06 (±0.2)
Warm humidified aerosol	14	Sodium, crystalline	30 (25-50)	0.08 (0.05-0.4)	0.16 (0.05-0.4)	0.10 (±0.4)

to the nebulizer at the end of each treatment to allow inhalation of most of the penicillin remaining in the nebulizer. The time was measured from the start of inhalation through the end of the last rinse. The mouth inhalation apparatus was used in all these tests. Since no appreciable difference in blood levels was noted in attempting to compare the Vaponefrin nebulizer plus the glass baffle attachment with the "small particle size" nebulizer, the particular type nebulizer used has not been indicated in Table 1. However, when the same patient was tested by the various methods listed, the same apparatus was used in each test. It can be seen that there is very little difference in the blood levels obtained by these various methods.

However, use of the water bottle increases the time required to complete the inhalation, thereby delaying the peak blood level

concentration of penicillin remaining in the nebulizer towards the end of an inhalation is approximately double the original concentration, hence the importance of rinses of the nebulizer at the end of each inhalation, even if the water bottle is used.

From Table 1 there appears to be no increase in blood level when the warm humidified aerosol method is compared with the cold dry aerosol method, except in the tests in which crystalline sodium penicillin aerosol was used. In six patients tested with both calcium penicillin and crystalline sodium penicillin with the cold dry and warm humidified methods, there was only a slight increase in blood levels with the warm humidified method, the time required for inhalation being essentially equal. However, in identical experiments using radioactive sodium aerosol, Talbot et al.³⁷ found a larger amount of the aerosol retained in the body, both locally and systemically, when the warm humidified

* Blood level determinations by the Hobby dilution method.

method was employed. In regard to the patient's comfort, inhalation of a warm humidified aerosol is preferred. It also has lessened the incidence of sore tongue reactions to penicillin.

The higher blood levels obtained with the

TABLE II
RESIDUES IN APPARATUS AFTER INHALATION OF 50,000
UNITS CALCIUM PENICILLIN

No. of Tests	Type of Nebulizer	Glass Baffle Attachment	Rebreathing Bag and Mouthpiece Attachment
30	Vaponefrin nebulizer 6,000 (2,500-10,000)	1,500 (1,000-2,000)	2,500 (500-8,000)
32	SPS nebulizer with fused mouthpiece 8,000 (5,000-20,000)	Rebreathing bag 2,000 (500-4,000)

crystalline penicillin salt are attributable as much to the lower residue remaining in the nebulizer after inhalation as to higher potency of the material. Penicillin used for test inhalations was dissolved on the day of use. Its potency was checked whenever there was any doubt. Some vials of crystalline penicillin contained more than the labeled number of units. Once the crystalline salt is dissolved it retains its potency when kept in the refrigerator for one week, but loses most of its potency in forty-eight hours at room temperature.

Penicillin assays of the residues remaining in various parts of the mouth inhalation apparatus after inhalation of 50,000 units calcium penicillin in 1 cc. normal saline, followed by two to three rinses of 0.5 cc. saline are shown in Table II. No significant difference was noted after various methods of inhalation, so that tabulations of methods as in Table I was not indicated. The difference between individual nebulizers in the numbered series seemed to be more important, especially in regard to the closeness of contact between the vertical capillary tube and the bottom of the nebulizer, as well as to how fine and uniform a mist the nebulizer

produced when judged by nebulization of methylene blue against a piece of blotting paper. It is seen from Table II that the residue of calcium penicillin in the apparatus averages 20 per cent of the original dose given. It is generally 5 to 10 per cent with crystalline penicillin salts.

TABLE III
RINSING EXPERIMENT—PENICILLIN RESIDUE IN VAPONEFRIN
NEBULIZER

	No. of Rinses	Time (Min.)	Residue (Units/Cc.)
Without Water Bottle			
Calcium penicillin.....	0	5:40	20,000
	1	8:37	20,000
	2	10:32	10,000
	3	13:18	2,000
Crystalline sodium penicillin	0	5:41	16,000
	1	8:30	5,000
	2	12:00	4,000
	3	14:30	1,250
With Water Bottle			
Calcium penicillin.....	0	6:45	10,000
	1	9:43	5,000
	2	14:17	1,250
	3	16:00	1,250
Crystalline sodium penicillin	0	6:45	10,000
	1	11:04	2,500
	2	14:57	2,000
	3	18:12	500

Table III shows the results of a controlled rinsing experiment, using the same Vaponefrin nebulizer to nebulize 50,000 units penicillin dissolved in 1 cc. normal saline at an oxygen flow of 10 liters per minute, varying the number of rinses of 0.5 cc. saline each, to compare residues with or without a water bottle connected to the regulator, and to compare residues when calcium penicillin or crystalline sodium penicillin is used. It can be seen that the use of the water bottle decreases the residue more appreciably when the calcium salt is employed than when the crystalline material is used. Time required for nebulization is increased by incorporation of a water bottle. Residues are

lower when the purer crystalline material is nebulized. For practical purposes, the results indicate that one rinse is sufficient if the water bottle is used, but otherwise at least two rinses should be used. Also an additional rinse should be used if crystalline penicillin is not available.

Blood level determinations following inhalation of penicillin aerosol using the mask nebulizer apparatus result in lower values than with the standard apparatus since the expired gas carries some penicillin aerosol with it to the outside air through the expiratory flutter valve. To obtain a blood level of 0.1 to 0.2 units per cc. the dosage should usually be 100,000 units penicillin in 2 to 4 cc. normal saline when the mask is used, followed by a 1 cc. rinse. Inhalations may be given four to five times daily.

With the continuous drip method, either attached to the mask or in the head tent, using concentrations of 5,000 to 10,000 units penicillin per cc. normal saline, blood levels averaging 0.05 to 0.1 unit per cc. are obtained for several hours with the interrupted type of treatment, using a total dosage of 100,000 to 300,000 units twice daily. With continuous slow nebulization of 1,000,000 units (concentration 10,000 units per cc. normal saline) over a twenty-four-hour period in the head tent, blood levels of 0.01 to 0.03 unit per cc. constantly have been found.

Recently a number of patients have been treated with penicillin aerosol using a foot-pump as a source of power for nebulization, instead of oxygen. This method³³ is economical, requires approximately the same length of time for nebulization and results in average penicillin blood levels of 0.1 to 0.2 unit per cc. for two hours after the start of test inhalations of 50,000 units followed by two saline rinses of 0.5 cc. each.

Use of a hypertonic 3 per cent saline solution as diluent for penicillin aerosol is now being investigated and the few preliminary

results show a tendency toward higher blood levels and possibly a more effective local deposition of the aerosol particles. Further studies are under progress at the present time, including a preliminary drying of the hypertonic aerosol particles by steam to decrease the particle size as they enter the upper respiratory tract, whereafter the particles become surrounded by water vapor. This results in an increase in size and weight of the particles as they reach the bronchioles and alveoli, which contributes to local deposition.³⁵

Our experience with diluents other than saline or distilled water for use in penicillin aerosol therapy has led to the conclusion that such substances as 1 per cent neosynephrine or Vaponefrin, 5 per cent glycerol, 5 per cent to 50 per cent propylene glycol or triethylene glycol and 0.1 to 0.2 per cent aerosol O.T. are not as efficacious. Use of the vasoconstrictor drugs results uniformly in lower blood levels and the absorption curve is not prolonged, although the peak of the curve may be delayed to one or one and a half hours after the start of inhalation. Various diluents which give a more stable mist have the disadvantage of increased viscosity in higher concentrations, which slows nebulization considerably and frequently plugs the nebulizer toward the end of the treatment. With the use of 5 per cent triethylene glycol, penicillin blood levels are about 30 per cent lower than when penicillin is dissolved in normal saline in comparable test inhalations on the same patients. In a small series of these patients, however, inhalation of radioactive sodium dissolved in 5 per cent triethylene glycol resulted both in greater local deposition of the aerosol and in increased absorption.³⁷

A few patients had blood level determinations made after intramuscular injections of penicillin for comparison with levels obtained after inhalation of penicillin aerosol. In general, two to three times as much

penicillin must be given by inhalation to insure as high a level of penicillin in the blood stream, although this varies to a considerable degree with the extent of the bronchopulmonary disease. Contrary to Segal's report,¹⁷ we find that normal individuals obtain higher blood levels after inhalation of penicillin than patients with chronic bronchopulmonary disease. The greater the involvement the lower the absorption, as a rule. In regard to lobar pneumonia it should be remembered that once consolidation is established, the benefit derived from penicillin aerosol is exerted through absorption of the drug into the blood stream in portions of uninvolved lung. We have obtained striking clinical improvement in a few patients with advanced bronchiectasis, pulmonary fibrosis and emphysema, who never had an effective penicillin blood level demonstrated after test inhalations. Furthermore, some patients failed to improve after massive doses of intramuscular penicillin, but subsequently improved on penicillin aerosol alone, although much lower blood levels were obtained, indicating the necessity for a therapeutically effective local concentration of penicillin. Apparently in some cases of bronchopulmonary suppuration in which bacteria grow on surfaces covered by fibrinopurulent exudate the capillary blood supply may be inadequate to insure a local therapeutic penicillin level, whereas inhalation of the drug insures adequate local concentration if the airway remains patent.

Although Knott and Southwell²⁹ reported a higher concentration of penicillin in arterial blood than in venous blood during penicillin aerosol administration, we failed to confirm these results, finding identical levels in a few instances in which simultaneous arterial and venous blood specimens were obtained. In their animal experiments these authors demonstrated a considerable concentration of penicillin in

lung tissue. They suggested the use of penicillin aerosol in an oxygen tent and reported results of the degree of penicillin absorption in nine children with minor respiratory infections. Clinical results in serious respiratory infections were not evaluated although early results looked promising.

Recently sputum specimens have been tested for assay of penicillin at various times after inhalation of penicillin aerosol and also after intramuscular administration of penicillin. Results thus far show that after single inhalation of 50,000 units penicillin, the concentration of penicillin sputum produced during the first one to four hours varies between 10 and 1,280 units per cc., with an average of 461 units per cc. With inhalation of 50,000 units penicillin dissolved in 5 cc. normal saline using the mask-nebulizer apparatus, one patient has shown a level of 640 units per cc. sputum for three hours after the time of administration of penicillin. Five patients failed to show demonstrable penicillin sputum levels after a single intramuscular injection. Twenty patients tested have shown no penicillin present in twenty-four-hour sputum samples while receiving 40,000 to 100,000 units of penicillin every 3 hours by intramuscular injection. In assays of total amount of sputum collected over a twenty-four-hour period from patients receiving 50,000 to 100,000 units penicillin aerosol four times daily, with the mouth inhalation apparatus, concentrations of 20 to 400 units per cc. sputum have been obtained. With the same dosage by mask nebulizer technic, penicillin sputum levels range from 10 to 245 units per cc. Two twenty-four-hour penicillin sputum assays in a patient receiving 900,000 units by slow continuous aerosol drip in an oxygen head tent over a twenty-four-hour period showed 1,600 and 640 units per cc. sputum, but two other tests were negative. The sputum jars for collections over more

TABLE IV
CLINICAL RESULTS OF PENICILLIN THERAPY IN BRONCHIECTASIS

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Weeks)
1	29	F	Pulmonary emphysema	1	slight	Inhalation	5,280,000	5
2	57	M	Bronchial asthma	1	marked	Inhalation	1,400,000	1
			Pulmonary emphysema	2	none	Inhalation	2,400,000	3
			Chronic sinusitis	3	slight	Inhalation	1,728,000	2.7
						Intramuscular	1,030,000	
				4	slight	Inhalation	4,350,000	5
						Intramuscular	3,180,000	1.7
3	62	M	Pulmonary emphysema	1	moderate	Inhalation	1,040,000	1.5
4	59	M	Pulmonary fibrosis	1	moderate	Intramuscular	1,200,000	1
				2	moderate	Inhalation	700,000	0.7
5	56	F	Pulmonary emphysema	1	marked	Inhalation	1,900,000	2.7
			Pulmonary fibrosis			Inhalation	950,000	0.7
				2	moderate	Inhalation	2,300,000	2
						Intramuscular	600,000	
				3	slight	Inhalation	2,440,000	2
						Subcutaneous	1,180,000	0.5
				4	slight	Oral	60,000,000	13
				5	none	Inhalation	500,000	0.5
6	21	M	Pulmonary emphysema	1	moderate	Inhalation	600,000	0.5
			Bronchial asthma			Intramuscular	700,000	1
				2	none	Inhalation	1,800,000	1.7
				3	slight	Inhalation	1,000,000	1
						Intramuscular	1,080,000	
				4	none	Oral	8,000,000	2
				5	marked	Inhalation	50,000 units 4 × daily	18 months
7	27	M	Bronchial asthma	1	marked	Inhalation	8,500,000	6
			Chronic sinusitis			Intramuscular	1,215,000	3
8	47	M	Bronchial asthma	1	none	Inhalation	540,000	0.7
			Pulmonary emphysema			Intramuscular	1,155,000	1.5
			Pulmonary fibrosis	2	none	Inhalation	3,250,000	8
			Rheumatoid arthritis			Oral	3,300,000	
						Intramuscular	7,650,000	
9	69	M	Pulmonary emphysema	1	moderate	Inhalation	1,300,000	1
			Chronic sinusitis					
10	60	M	Bronchial asthma	1	moderate	Inhalation	1,300,000	1
			Pulmonary emphysema			Intramuscular	1,000,000	
				2	slight	Inhalation	2,000,000	2
				3	slight	Inhalation	1,000,000	1.5
						(crystalline sodium penicillin)		
11	18	M	Chronic sinusitis	1	moderate	Inhalation	2,800,000	1.5
						Intramuscular	4,350,000	
				2	marked	Inhalation	3,525,000	2.3
				3	marked	Inhalation	30,000,000	30
				4	moderate	Inhalation	2,500,000	1.5
						Inhalation	600,000	0.5
						(Nasal Suction)		
12	52	M	None	1	slight	Intramuscular	1,475,000	1
						Inhalation	1,500,000	
13	67	F	Pulmonary emphysema	1	marked	Intramuscular	1,700,000	1.5
						Inhalation	1,750,000	

TABLE IV (Continued)

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Weeks)
14	18	F	None	1	moderate	Inhalation	6,750,000	3
15	55	F	Chronic sinusitis	1	moderate	Intramuscular	1,600,000	3
				2	moderate	Oral	6,000,000	1.5
				3	slight	Oral	7,000,000	1.5
16	60	M	Pulmonary emphysema Pulmonary fibrosis	1	none	Inhalation	500,000	2
						(Nasal Suction)		
						Intramuscular	1,450,000	2
17	59	F	Chronic sinusitis Rheumatoid arthritis	1	slight	Intramuscular	960,000	1
						Inhalation	480,000	0.7
18	54	F	Pulmonary emphysema Pulmonary fibrosis	1	none	Intramuscular	800,000	0.7
						Inhalation	2,650,000	2
19	46	M	None	1	slight	Intramuscular	3,230,000	2.5
						(Nasal Suction)	1,800,000	2.5
20	21	F	Pulmonary emphysema Nutritional edema	1	slight	Intramuscular	4,000,000	4
						Inhalation		
21	71	M	Pulmonary emphysema Pulmonary fibrosis	1	marked	Intramuscular	1,250,000	0.8
						Inhalation		
22	21	M	None	1	moderate	Intramuscular	900,000	28
						Inhalation	1,120,000	1
23	9	F	Pulmonary emphysema Chronic sinusitis	1	moderate	Intramuscular	2,800,000	2
						Inhalation	2,800,000	2
24	48	M	Bronchogenic carcinoma	1	moderate	Intramuscular	1,680,000	2
						Inhalation		
25	27	M	Chronic sinusitis	1	moderate	Intramuscular	3,000,000	2.5
						Inhalation		
26	16	M	Chronic sinusitis	1	moderate	Intramuscular	700,000	1
						Inhalation	3,000,000	2
27	24	F	Chronic sinusitis	1	moderate	Intramuscular	4,500,000	4.5
						Inhalation		
28	28	F	Chronic sinusitis	1	marked	Intramuscular	5,250,000	5
						Inhalation	9,000,000	9
29	25	F	Pulmonary emphysema Chronic sinusitis	1	slight	Intramuscular	1,120,000	1
						Inhalation	3,000,000	3
30	27	M	Pulmonary emphysema Chronic sinusitis	1	moderate	Intramuscular	22,500,000	20
						Inhalation		
31	16	F	None	1	marked	Intramuscular	18,000,000	17
						Inhalation		
32	33	F	None	1	marked	Intramuscular	360,000 pre-op.	0.3
						Intramuscular	2,520,000 postop.	1.6
33	16	M	Suppurative broncho-pneumonia Chronic sinusitis	1	slight to moderate	Intramuscular	12,000,000	9
						Intramuscular	49,000,000	3.5
34	57	M	Pulmonary emphysema	1	moderate	Intramuscular	7,000,000	1
						Intramuscular	7,200,000	2.5
35	70	M	Pulmonary emphysema Cardiac insufficiency (ASHD and ? cor pulmonale)	1	moderate	Intramuscular	3,500,000	3
						Intramuscular	4,500,000	5

TABLE V
EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN BRONCHIECTASIS

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
1	1	Hemolytic Strep. Non-hemolytic Strep. Staph. aureus	None	Decrease in cough and expectoration. No change in chest x-rays before and after treatment
2	1	Strep. viridans	B. pyocyaneus	Marked improvement in all symptoms, sustained only one month
	2	Strep. viridans	B. pyocyaneus B. aerogenes	Asthma became intractable
	3	B. pyocyaneus	B. pyocyaneus	Subsequent courses of penicillin gave slight and temporary benefit
3	4	Hemolytic B. pyocyaneus Strep. viridans	Hemolytic B. pyocyaneus B. aerogenes	Decrease in cough and expectoration and dyspnea, but improvement sustained only one month
4	1	Hemolytic Strep. Strep. viridans Staph. albus	B. aerogenes	No improvement on course of 1 week I.M. penicillin, but temporary improvement with both courses of aerosol. Treatment discontinued twice because of urticaria and sore, reddened tongue and throat
5	2	None	None	Increased cough on sodium penicillin aerosol
	1	Strep. viridans	Strep. viridans	Pruritus on intramuscular penicillin.
	2	Strep. viridans	Strep. viridans	Local soreness and blisters at S.C. injection sites
	3	No growth	B. aerogenes	Prolonged course on oral penicillin at home with slight benefit
	4	None	None	Bronchial relaxation program most helpful
6	5	Strep. viridans	B. coli	Benefit not sustained
	1	Strep. viridans	None	Sore, reddened throat on sodium salt, increased asthma and pulmonary edema
	2	Strep. viridans	B. aerogenes	Edema of feet and ankles; urticaria
	3	None	B. aerogenes	No change in symptoms
	4	Strep. viridans	B. aerogenes	
	5	Strep. viridans Staph. aureus	B. coli Occasional Strep. viridans	Remarkable and sustained improvement throughout period of continuous therapy. No other medication necessary except for occasional Vaponefrin or oral aminophyllin
7	1	Strep. viridans Staph. aureus	B. aerogenes	Reddened sore throat and irritative cough on sodium salt. Improvement in all symptoms except those due to sinusitis
8	1	Strep. viridans	B. aerogenes B. coli	Increased cough on sodium salt. Soreness at injection sites. Intractable asthma unchanged. No change in symptoms
9	2	Strep. viridans	B. aerogenes	Decrease in cough and expectoration
10	1	Pneumococcus, type 12 Strep. viridans	B. coli B. coli	Developed fever, urticaria, aggravation of asthma and sore, reddened tongue
	2	Strep. viridans	B. aerogenes	Sore reddened tongue, aggravation of asthma
	3	Non-hemolytic Strep.	B. coli	Decrease in cough and expectoration but increase in dyspnea and wheezing
11	1	Staph. albus	B. aerogenes	Penicillin stopped because of urticaria.
	2	Hemolytic Strep.	B. aerogenes	Improvement sustained 5 months
	3	Gram-pos cocci Gram-pos. and neg. bacilli	Gram-neg. bacilli	Had course of 1,200,000 units streptomycin aerosol prior to penicillin therapy
				Improvement sustained by continuous penicillin aerosol treatment at home during winter and spring

TABLE V (Continued)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
	4	Staph. albus Strep. viridans	B. aerogenes	0.25% p-chlorophenol used as diluent for penicillin, but provoked irritative cough during first week. Sustained improvement less marked than previously
12	1	Strep. viridans	None	Urticaria necessitated stopping therapy
13	1	None	B. coli † B. aerogenes †	Cough became non-productive
14	1	H. influenzae	B. aerogenes Strep. viridans	Aerosol pre-operatively. I.M. penicillin following left lower lobe lobectomy. Febrile postoperative course with repeated thoracenteses (fluid sterile). Follow-up unremarkable
15	1	Staph. albus Strep. viridans	None	Symptomatic improvement
	2	H. hemolyticus H. influenzae	B. coli B. aerogenes H. influenzae	Temporary improvement. Rales less numerous
	3	Staph. albus Strep. viridans	None	Symptomatic improvement without change in sinus x-rays
16	1	None	None	Urticaria on I.M. penicillin. Bronchial relaxation program helpful
17	1	Strep. viridans	None	Urticaria
18	1	None	B. coli B. aerogenes	Urticaria
	2	Strep. viridans	None	Urticaria
19	1	None	None	Decrease in cough and expectoration. Improvement not sustained
20	1	Hemolytic Staph. aureus Staph. albus	Strep. viridans	Striking improvement attributed chiefly to general supportive measures
21	1	Strep. viridans	B. coli Few Staph. aureus	Marked decrease in cough and expectoration; improvement in general well-being with progressive weight gain. Benefit sustained by weekly inhalations without additional medication for past 6 months
	2	D. pneumoniae	B. coli	Cough became non-productive. X-ray clearing of bronchopneumonia
22	1	Strep. viridans	B. coli	
23	1	None	None	Had left pneumonectomy several years ago for bronchiectasis. Advanced bronchiectasis in remaining lung. Penicillin aerosol, with continuous treatment at home, keeps patient ambulatory. Sinus and chest x-rays unchanged. Now on sodium sulfacetimide aerosol
	2	Pneumococcus, type 6	Strep. viridans Non-hemolytic Strep. H. influenzae	
		D. pneumoniae	H. influenzae B. coli	
24	1	Staph. aureus Non-hemolytic Strep.	None	Marked symptomatic improvement on aerosol therapy pre-operatively. Uneventful postoperative course (pneumonectomy) on I.M. penicillin
25	1	D. pneumoniae Strep. viridans	B. aerogenes	Decrease in cough and expectoration, sputum losing foul odor
26	1	Hemolytic Strep. *	B. coli †	Case of minimal bronchiectasis, with involvement of both lower lobes, became asymptomatic. Later non-productive cough recurred, but less severe
	2	None	Strep. viridans	Minimal bronchiectasis. All symptoms disappeared on penicillin aerosol. Benefit sustained 6 months
27	1	Non-hemolytic Strep. Staph. aureus	B. coli	

TABLE V (Continued)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
28	1	Hemolytic Strep. Non-hemolytic Strep. Staph. aureus	B. coli B. aerogenes Occasional Staph. aureus	Failed to improve on previous course of 4,000,000 units I.M. penicillin. Sustained improvement on continuous penicillin aerosol therapy prior to LLL lobectomy. Uneventful postoperative course on I.M. penicillin. Follow-up of 6 months unremarkable
29	1	Staph. aureus	Staph. aureus	Advanced bilateral bronchiectasis. Unable to continue therapy because of dyspnea and general weakness, despite bronchodilator adjuvants. To be tried later with mask-nebulizer apparatus
30	1	D. pneumoniae Staph. aureus	Staph. aureus B. coli	Advanced cylindrical and saccular bilateral bronchiectasis. Relapsed in all symptoms whenever therapy was interrupted for longer than one week, despite substitution of 10% sodium sulfacetimide aerosol. Intermittent reactions of sore tongue and irritative cough on calcium salt. No reaction to crystalline sodium salt
31	2	Gram-neg. bacilli	Gram-neg. bacilli	Status quo maintained on 15% sodium sulfacetimide aerosol 1 cc. t.i.d. for 4 weeks
	1	Hemolytic Strep. Staph. aureus	B. aerogenes Few Staph. aureus	Sustained improvement on continuous therapy at home preliminary to lobectomy of RLL with decreased cough and expectoration, sputum losing foul odor and much of purulent element. Developed postoperative foul empyema with bronchopleural fistula requiring thoracotomy for drainage 2 weeks later. Spiking febrile course subsided 3 days later. Discharged to be followed in surgical OPD 6 weeks after admission with sinus tract still open but only slight drainage. Mild residual cough and expectoration persist
	2	None	Gram-neg. bacilli	Past history of aspirated tack in childhood removed by bronchoscopy. Repeated hemoptyses led to admission. Bronchography following bronchoscopy demonstrated bronchiectasis of RLL and of one posterior segment of LLL. Continued penicillin aerosol therapy at home following discharge. Sustained improvement for 2 months with diminished cough and expectoration. Sputum became mucoid in consistency
32	1	Strep. viridans Staph. albus Non-hemolytic Strep.	Strep. viridans N. catarrhalis Gram-neg. bacilli	Acute episode of diffuse bilateral bronchopneumonia caused by hemolytic Staph. aureus resistant to penicillin in concentration of 5 U/cc. Marked progressive improvement after substitution of aerosol for I.M. penicillin given for first week by continuous aerosol drip. Staph. aureus reappeared when 15% sulfacetimide aerosol was substituted and disappeared again when combined penicillin and sulfacetimide aerosol was instituted with 4 inhalations daily
33	1	Hemol. Staph. aureus	Hemol. Staph. aureus	
	2	Hemol. Staph. aureus	Gram-neg. bacilli	

TABLE V (Continued)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After treatment	
34	1	Hemolytic Strep. Strep. viridans (Bronchoscopic aspiration)	Hemolytic gram-neg. bacilli	Advanced saccular bronchiectasis of both lower lobes resulting from unresolved pneumonia coincident with aspiration of chicken bone 5 years ago. Foreign body not visualized on repeated bronchoscopies, but was coughed up 4 years ago at time of single hemoptysis. Intratracheal instillation of penicillin 2 years ago without appreciable benefit. Temporary improvement on short course of I.M. penicillin. More striking improvement on aerosol therapy, sputum decreasing from 6 ounces daily of foul purulent material to 3-4 ounces daily of non-foul thinner sputum with less cough and dyspnea. Streptomycin aerosol to be combined with penicillin in near future
35	1	Staph. aureus	Gram-neg. bacilli Few Staph.	Marked decrease in dyspnea, cough and expectoration, sputum diminishing from over 1 ounce daily to less than $\frac{1}{2}$ ounce, becoming less purulent and losing foul odor

* Nose culture.

† Throat culture.

than a three-hour period are surrounded by ice in a bowl to prevent loss of penicillin activity.

Bobrowitz, Edlin et al.³⁸ reported similar penicillin sputum levels after intratracheal instillation or nebulization of penicillin, but did not find sputum levels after intramuscular administration of penicillin except in one case in which the level was only 0.4 units per cc. White³⁹ reported no detectable penicillin sputum level after intramuscular administration.

An interesting study by Humphrey and Joules²⁷ revealed that penicillin was rarely found in the sputum in cases of bronchitis and bronchiectasis after intramuscular injection of the drug whereas it was present in considerable quantities after inhalation of penicillin aerosol for periods of six hours or more. These authors report that in patients with lobar pneumonia, small amounts of penicillin were recovered from the sputum

after intramuscular injection during the active phase of the disease; but when the consolidation cleared and a chronic bronchitis persisted, no penicillin could be detected after intramuscular injection of penicillin, although the patient continued to cough up considerable amounts of expectoration.

We are continuing studies on penicillin sputum levels to compare values obtained with identical dosage of penicillin aerosol and penicillin by intramuscular injection in the same patients.

The problem of penicillin-resistant microorganisms has not yet become alarming in patients treated by aerosol therapy over prolonged periods, except in some instances of *Staphylococcus aureus* infection in children with pancreatic disease reported by Andersen and di St. Agnese.²⁴

The use of various sulfonamide aerosols for eradication of gram-negative organisms

has been disappointing in our experience, but further trials with larger dosage are in progress. Recently we have been using streptomycin aerosol in cases of mixed infection or in cases showing original predominance of gram-negative bacteria. Sputum streptomycin levels are demonstrable after inhalation of the drug, but not after intramuscular injection in the small series studied thus far. Olsen²² has shown that some cases of bronchiectasis respond better to a combination of penicillin and streptomycin aerosol.

One of our patients developed an antipenicillin substance in her serum after one year of sporadic penicillin aerosol therapy for sinusitis and infectious bronchial asthma. Since she originally obtained fairly constant blood levels of 0.05 to 0.2 unit per cc. serum after inhalation of 50,000 units, and later no blood bacteriostatic activity, her serum was tested with known amounts of added penicillin. It was found that the added penicillin was completely inhibited. The antipenicillin substance was not affected by a temperature of 60°C., but was destroyed at a temperature of 80°C. No antipenicillin substance was found in this patient's sputum, since she obtained a penicillin sputum level as high as 1,280 units per cc. for one hour after inhalation of 50,000 units. She has recently improved markedly after two weeks' treatment with nasal penicillin aerosol and intermittent negative pressure for exacerbation of chronic sinusitis. Ten other patients who have received prolonged penicillin aerosol therapy, as well as three control subjects have had their sera tested, but none have shown evidence to date of antipenicillin activity.

The clinical results of penicillin aerosol in therapy of bronchiectasis and its effect on sputum cultures are seen in Tables iv and v. Of fifty-nine courses of therapy in thirty-five patients, twenty-six of whom had bilateral disease with involvement of two or

more lobes, there was marked improvement in fifteen, moderate in twenty-two, slight in fourteen and no improvement in eight. Only four patients were considered operable. These cases showed marked or moderate improvement on preoperative penicillin aerosol, but one developed a postoperative empyema despite instillation of penicillin into the pleural cavity at operation and use of postoperative intramuscular penicillin. The remaining five had disease minimal enough to warrant further follow-up on conservative treatment, and to date have continued to do well. Where sputum cultures were compared before and after courses of penicillin aerosol therapy, gram-negative bacilli predominated in forty-three with disappearance of the original gram-positive organisms, whereas only thirteen showed the presence of some gram-positive organisms after treatment.

Tables vi and vii show the clinical results and sputum cultures in penicillin treatment of eight patients with lung abscess. Of seven courses of therapy in five patients with the diagnosis of acute lung abscess, marked improvement occurred in four, slight improvement in two, and no improvement in one. Four of the five patients had complete clinical and x-ray recovery, whereas one required surgical drainage which was followed by recovery. Of four courses of therapy in three patients with chronic lung abscess, two resulted in marked improvement, one in slight improvement, and one showed no change. The latter patient later had a lobectomy. The one patient who twice showed marked improvement on penicillin aerosol therapy has remained well for seven months. The final outcome of the patient showing only slight temporary improvement is not known. Sputum cultures showed gram-positive organisms prior to penicillin treatment and gram-negative bacilli after treatment.

Results of penicillin therapy in treatment

TABLE VI
CLINICAL RESULTS OF PENICILLIN THERAPY IN LUNG ABSCESS

Case No.	Age	Sex	Type	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
							Route	Total Dosage	Duration (Weeks)
1	35	F	Acute	Rheumatic heart disease	1	slight	I.M.	4,480,000	4.2
2	43	M	Chronic	Pulmonary infarction	2	marked	I	1,600,000	1.1
				Bronchiectasis	1	slight	I	740,000	1
				Pulmonary fibrosis					
3	24	M	Chronic	Bronchiectasis	1	none	I	6,000,000	4.2
4	61	M	Acute	Suppurative bronchopneumonia	1	marked	I	1,600,000	1.1
5	65	M	Acute	Bronchiectasis	1	slight	I	2,650,000	1.5
					2	none	I	5,875,000	2.3
							I.M.	2,030,000	4
6	40	F	Acute	None	1	marked	I.M.	3,360,000	3
7	16	M	Acute	Suppurative bronchopneumonia	1	marked	I	6,250,000	3.5
							I.M.	8,000,000	3.5
							I	15,200,000	6.5
8	45	M	Chronic	None	1	marked	I	1,000,000	1.5
					2	marked	I	3,000,000	3

I—Inhalation.

I.M.—Intramuscular.

TABLE VII
EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN LUNG ABSCESS

Case No.	Course	Sputum Culture		Remarks
		Before Treatment	After Treatment	
1	1	Hemolytic Staph. aureus	None	Abscess persisted on I.M. penicillin. Recovery with aerosol, although I.M. penicillin given later because of a second small pulmonary infarct
2	1	Strep. viridans	No Strep.	Slight increase in vital capacity. Chest x-rays unchanged
3	1	Hemolytic Strep.	B. proteus	Aerosol preoperatively. Lobectomy necessary, with subsequent recovery
4	1	Hemolytic Staph. aureus Strep. viridans	B. aerogenes	Previous courses of I.M. penicillin for 1 month, with increasing pneumonitis. Improvement began on aerosol therapy, and recovery occurred on combination of aerosol and I.M. penicillin
5	1	Strep. viridans	None	Moderate symptomatic improvement, but x-rays unchanged. Required surgical drainage of abscess with subsequent recovery
6	2	Strep. viridans	B. aerogenes	Slow improvement until penicillin was nebulized with helium-oxygen mixture, following which recovery occurred, with complete x-ray clearing
	1	Strep. viridans	None	
7	1	Staph. albus Strep. viridans Hemolytic Staph. aureus	B. coli B. aerogenes	No improvement on I.M. penicillin alone. Improvement began on aerosol therapy, but was most striking when 3 weeks later helium-oxygen mixture was used to nebulize penicillin, after demonstration of a nonaerated right middle lobe by bronchoscopy and bronchography. Complete x-ray clearing, without residual abscess cavity or bronchiectasis by lipiodol studies
8	1	D. pneumoniae	B. aerogenes	Recurrence of cough and expectoration 6 weeks after first course. Symptomatic improvement and progressive x-ray clearing as result of second course. No recurrence in 7 months
	2	Hemolytic Strep. Strep. viridans	Strep. viridans	

of sixteen patients in whom the primary diagnosis was chronic bronchitis are shown in Tables VIII and IX. Of twenty-four courses

were obtained after penicillin treatment gram-positive organisms were still present in only three cases, whereas the others showed

TABLE VIII
CLINICAL RESULTS OF PENICILLIN THERAPY IN CHRONIC BRONCHITIS

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Days)
1	57	M	1	marked	I	2,240,000	12
2	36	F	1	none	I	1,230,000	7
				2	none	O	7,400,000	15
3	66	F	Acute pharyngitis	1	moderate	I	300,000	3
4	35	F	1	moderate	I	3,500,000	18
						I.M.	3,200,000	14
5	46	M	Pneumonitis	1	marked	I	1,300,000	7
						O	5,700,000	10
6	62	M	Chronic sinusitis	1	moderate	S.C.	1,260,000	8
			Pulmonary fibrosis			I.M.	2,230,000	11
			Pulmonary emphysema			I	2,550,000	
7	52	M	Chronic sinusitis	1	none	I.M.	2,715,000	22
						I	5,500,000	11
8	16	M	Chronic sinusitis	1	marked	I.M.	1,000,000	5
						I (N.S.)	2,700,000	8
9	15	M	Chronic sinusitis	1	marked	I (N.S.)	8,325,000	23
						I.M.	3,010,000	25
				2	marked	I (N.S.)	1,600,000	8
10	70	M	Acute bronchitis	1	slight	I	2,650,000	6
			Chronic sinusitis			O	4,900,000	9
11	58	F	Chronic sinusitis	1	marked	I	3,000,000	10 months
			Pulmonary emphysema					
				2	marked	I	1,500,000	10
12	53	M	Pulmonary tuberculosis	1	marked	O	5,000,000	10
				2	marked	I.M.	2,100,000	7
						(beeswax)		
13	78	M	1	marked	I	3,800,000	19
14	73	M	1	moderate	I	2,000,000	10
				2	moderate	I	2,000,000	8
						O	1,250,000	8
15	24	F	1	moderate	I	1,000,000	7
				2	moderate	I	1,500,000	10
						I.M.	1,000,000	
				3	moderate	I	2,000,000	10
						I.M.	1,400,000	
16	30	M	Chronic sinusitis	1	marked	I (N.S.)	500,000	2
				2	marked	I	1,400,000	2

I—Inhalation.

I.M.—Intramuscular.

O—Oral.

I (N.S.)—Inhalation (nasal suction).

of therapy, improvement was marked in twelve, moderate in eight, slight in one, while three resulted in no improvement. In fifteen courses in which sputum cultures

gram-negative bacilli predominating.

Detailed case reports with illustrative chest x-ray photographs are presented below:

TABLE IX

EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN CHRONIC BRONCHITIS

Case No.	Course	Sputum Culture		Remarks
		Before Treatment	After Treatment	
1	1	Pneumococcus, type 6	None	Previous course of I.M. penicillin ineffective. No recurrences for 18 months
2	1	Strep. viridans	Strep. viridans	Reaction: sore, reddened tongue and throat. Recurrent bronchopneumonia but bronchography negative
	2	Strep. viridans	None	Rapid improvement
3	1	Hemolytic Strep.	No hemolytic Strep.	Bronchial relaxation relieved bronchospasm which developed after discharge from hospital
4	1	None	B. aerogenes	No recurrence in 1 year
5	1	Pneumococcus, type 17	B. aerogenes	Recurrent pneumonitis cleared entirely. No recurrence for over 1 year
6	1	Strep. viridans	B. aerogenes	Reaction: increased cough and bronchospasm
7	1	Hemolytic Strep. Strep. viridans H. influenzae	B. aerogenes	
8	1	B. proteus	B. aerogenes	Possible bronchiectasis (bronchography refused)
9	1	Staph. albus	B. aerogenes	Probable bronchiectasis (bronchography refused). Required bronchial relaxation program on first admission. Improvement sustained over 1 year
	2	Strep. viridans	B. coli	
10	1	No growth	B. aerogenes B. coli	Reaction: sore, red tongue and throat, increased cough temporarily. Marked improvement from bronchial relaxation program
11	1	Strep. viridans Staph. aureus	Strep. viridans	Possible bronchiectasis (refused bronchography). Symptoms controlled by 1-2 inhalations weekly in clinic. Improved on aerosol therapy at home, following exacerbation of symptoms
	2	Staph. aureus Strep. viridans	Gram-neg. bacilli	
12	1	Hemolytic Strep.	B. proteus	Recurrence 6 months later
	2	Hemolytic Strep. Staph. aureus	None	Reaction: Urticaria. No recurrence in 6 months
13	1	Strep. viridans Staph. albus	None	Bronchial relaxation very beneficial. No recurrence in 6 months
14	1	Hemolytic Strep. D. pneumoniae	N. catarrhalis	Bronchial relaxation helpful. Recurrence of moderate degree later. Reaction: sore reddened tongue on calcium penicillin, but not on crystalline sodium penicillin
	2	Hemolytic Strep.	Strep. viridans	Gradual recurrence of symptoms. Mild bronchospasm. Continued to improve on subsequent courses
15	1	Hemolytic Strep. Strep. viridans	None	
	2	Staph. aureus H. influenzae	None	
16	1	Staph. aureus Hemolytic Strep. Non-hemolytic Strep.	Gram-neg. bacilli	Sinusitis remained improved, although chronic cough and expectoration persisted. Bronchography failed to demonstrate bronchiectasis despite suggestive history and persistent rales over left lower lobe. Symptoms partially relieved by occasional test inhalations and markedly relieved by longer course of therapy
	2		Gram-neg. bacilli	

CASE REPORTS

CASE 1. (C. A.). The patient, a nineteen year old man, had chronic cough and expectoration and symptoms of mild, chronic sinusitis since the age of nine years. His past history included pertussis and bronchial asthma in early childhood. Three years ago symptoms became more severe, sputum increasing in amount to 3 to 4 ounces daily of yellowish-brown purulent, occasionally blood-streaked material. Two years ago a single hemoptysis occurred of 8 ounces of bright red blood.

Bronchoscopy and bronchography in January, 1945, demonstrated advanced bronchiectasis of the right middle lobe and left lower lobe and early bronchiectasis of the right lower lobe. Surgery was suggested but refused.

On admission to the hospital two months later the patient did not appear ill. The vital signs were normal. Positive physical findings included slight congestion of the nasal mucosa, moderate injection of the pharynx and shotty posterior cervical lymph nodes. Chest appeared symmetrical with good bilateral expansion. Lungs were hyperresonant anteriorly above the level of the fourth rib and resonant elsewhere, with no change in breath sounds or fremitus. There were numerous coarse and medium moist râles over the left lower lobe and a moderate number of similar râles at the right posterior base and over the right middle lobe. The extremities showed moderate clubbing.

Laboratory data revealed the following: Red blood cells 5,700,000; hemoglobin 16.7 Gm.; white blood cells 14,100 with a normal differential count. The sedimentation rate was normal. Sputum culture: *Staph. albus* predominating.

Intensive combined penicillin therapy was instituted in conjunction with postural drainage twice daily. Intramuscular penicillin was given in dosage of 50,000 units every three hours for a total of 4,350,000 units. Calcium penicillin aerosol was given with the usual mouth inhalation apparatus, 50,000 units in 1 cc. normal saline every four hours for a total of 2,800,000 units. Penicillin blood levels obtained after single test inhalations were: 0.1 U/cc. serum one-half hour after start of inhalation, 0.05 U/cc. serum at one, one and one-half and two hours.

The urinary excretion of penicillin in the six hours following inhalation was 13 per cent of the amount administered. At the onset of therapy the patient was raising 5 to 6 ounces daily of purulent, slightly foul, blood-streaked sputum, half of which was raised on postural drainage. After a few days cough and expectoration decreased about 50 per cent and the sputum lost its odor, becoming thinner in consistency with rare streaks of blood. Sputum culture: *B. aerogenes* predominating, no *Staph. albus*. Râles persisted especially over the left lower lobe but were less coarse and less numerous. The patient was afebrile and ambulatory. On the eleventh day the patient developed generalized urticaria necessitating cessation of all penicillin therapy. The reaction subsided in four days. The patient was discharged moderately improved to continue on a regimen of oral sulfadiazine and neosyneprine-sulfathiazolate by inhalation.

Following discharge the patient worked at a newsstand and did fairly well clinically until six months later when cough and expectoration increased following an acute respiratory infection. He was readmitted for further antibiotic aerosol therapy. Sputum culture: Hemolytic streptococci predominating. Complete blood count and sedimentation rate were normal. Râles persisted at both lung bases.

He was given a course of crude streptomycin aerosol, 200,000 units in 4 cc. distilled water twice daily for a total of 2,800,000 units in one week. No blood level was detected with this dose, but a blood level of 1.5 U/cc. serum was obtained five hours after the start of a test inhalation of 400,000 units. Sputum specimen obtained before the usual 200,000 units dose showed *H. influenzae* and *N. catarrhalis* and a few colonies of non-hemolytic streptococci on culture, whereas a specimen obtained after inhalation showed only a moderate growth of non-hemolytic streptococci.

Following the course of streptomycin aerosol, penicillin aerosol was given for fifteen days with a daily dosage of 225,000 units or a total of 3,525,000 units. Penicillin blood levels comparable with those on the first admission were obtained. Final sputum culture: *B. aerogenes*. Sputum had decreased from 3 ounces to 1 ounce

daily at the time of discharge from the hospital.

In the next interval of seven months at home the patient took daily penicillin aerosol inhalations 50,000 units three times a day for a total of 30,000,000 units.

At the end of this period he was hospitalized for re-evaluation. Sputum cultures: *B. aerogenes* or *E. coli* predominating. Physical signs over the left lower lobe were unchanged, but only a few fine and medium post-tussic râles were audible at the right posterior and anterior bases. Sputum measured 2 to 3 ounces daily of purulent, non-foul, non-bloody material. Sinus x-rays revealed mild maxillary and ethmoid sinusitis. Bronchography was repeated and reported as showing cylindrical bronchiectasis of the left lower lobe only, although the right middle lobe was not completely filled. It was believed that there possibly was slight improvement in the bronchographic findings, despite difference in technic, compared with the earlier films.

Since the patient's family still refused any surgical procedure, a course of calcium penicillin aerosol, 50,000 units dissolved in 1 cc. of 0.25 per cent parachlorophenol five times daily was given over an eighteen-day period for a total of 4,250,000 units. During the last five days an additional 50,000 units was given four times daily by the nasal aerosol-negative pressure apparatus for a total of 1,000,000 units. Sputum culture showed only a few colonies of gram-negative bacilli, which were sensitive to a 1:2,000 dilution of para-chlorophenol. At the start of therapy using para-chlorophenol as a diluent, the patient complained of increased dry, irritative cough which later subsided. Sputum decreased to 1 to 1.5 ounces daily, and the patient was discharged improved. He has continued aerosol therapy at home using penicillin dissolved in normal saline for the past five months, continuing to work without any exacerbation of symptoms.

CASE 2. (M. R.*). The patient, a twenty-one year old white man, had advanced bilateral bronchiectasis, pulmonary emphysema and bronchial asthma dating back to childhood.

* This case was previously reported in part by the authors in the *New York State J. Med.*, 46: 1703, 1946.

Symptoms became more severe after the age of fourteen years. Bronchograms demonstrated marked cylindrical and saccular bronchiectasis of both lungs. (Fig. 5.) Chest x-ray (Fig. 5) prior to institution of continuous penicillin aerosol therapy showed persistent peribronchial pneumonitis. The patient failed to obtain any sustained improvement on a regimen of postural drainage, regular bronchoscopic aspirations, oral sulfonamides, repeated courses of intramuscular penicillin, oral penicillin and intermittent courses of penicillin aerosol and various sulfonamide aerosols. Numerous hospitalizations were necessary.

Since June, 1945, the patient has been on continuous calcium penicillin or crystalline sodium penicillin aerosol therapy at home, followed in the out-patient department with a daily dosage of 200,000 units divided into four inhalations. He began to show improvement after the first six weeks, since when clinical improvement has been more or less progressive and sustained. Test penicillin blood levels after inhalation of 50,000 units show 0.05 U/cc. serum at the end of one-half hour, 0.05 U/cc. at one hour, and 0.025 U/cc. at two hours. Figure 6 shows chest x-rays taken after institution of aerosol therapy with marked clearing after four months on continuous therapy and less striking x-ray improvement at the end of sixteen months. The clinical improvement, however, has been striking throughout the eighteen-months course thus far. Cough is rarely troublesome and is productive of only 1 to 2 ounces mucopurulent material daily compared to the original amount of 8 ounces purulent sputum daily. Sputum cultures generally show only gram-negative bacilli, although rarely *Strep. viridans* or *Staph. aureus* have been cultured. There has been a weight gain of 35 pounds. Asthma has not been troublesome, rarely requiring use of the Vaponefrin spray or oral aminophyllin. Mild activity does not produce dyspnea, whereas prior to treatment the patient could not walk across the room without dyspnea. Vital capacity has increased from 1,200 to 2,200 cc. During the past seven months the patient has worked four hours daily, as a clerk, for the first time in his life.

Despite the prolonged use of penicillin the



FIG. 5. Case 2. A and B, bronchograms in 1944 revealing advanced cylindrical and saccular bronchiectasis of all lobes. Chest x-ray (bottom right) in 1944 prior to continuous penicillin aerosol therapy, demonstrating bilateral peribronchial pneumonitis, pulmonary fibrosis and emphysema.

gram-positive organisms occasionally obtained on sputum culture have not become penicillin-resistant. Attempts to lower the daily dosage below 200,000 units have resulted in increased cough and expectoration within five to seven days. Attempts to substitute 15 per cent sodium sulfacetimide aerosol have likewise resulted in exacerbation of symptoms within ten days, with gram-positive organisms reappearing on culture of the sputum. Since *E. coli* cultured from his sputum was shown to lessen the growth-inhibiting power of penicillin by 40 to 50 per cent in two hours, 1 cc. of 15 per cent sodium sulfacetimide has been added to each inhalation of penicillin aerosol for six months, without effect

on the presence of gram-negative bacilli. Subsequently 1 cc. of 30 per cent sodium sulfacetimide was added to the penicillin aerosol without eradication of gram-negative bacilli from the sputum.

At the time of the last chest x-ray (Fig. 6) considerable puddling of secretions in the cystic areas was noted. Physical examination revealed occasional expiratory rhonchi toward the right base, numerous coarse and medium moist râles persisting over the lower half of the right chest and fewer finer râles over the lower half of the left chest. The patient was advised not to neglect postural drainage on arising and retiring and started taking aminophyllin 0.2 Gm. on arising

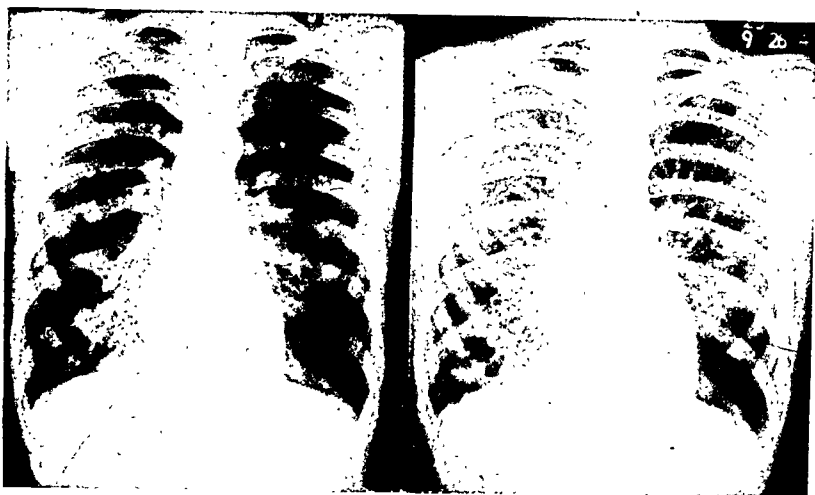


FIG. 6. Case 2. Chest x-ray (left) taken four months after institution of continuous penicillin aerosol therapy reveals marked clearing of pneumonitis secondary to bronchiectasis. Chest x-ray (right) taken one year later shows less marked clearing with some retention of secretions in cystic areas in right lower lung field.

and at night when necessary. The patient's blood serum shows no antipenicillin activity despite prolonged therapy. Penicillin sputum level was 640 U/cc. for one hour after inhalation of 50,000 units. One week ago streptomycin aerosol (2 Gm. daily) was substituted for penicillin aerosol for a course of therapy, sodium sulfacetimide being discontinued. A twenty-four-hour sputum assay revealed 280 units streptomycin per cc. 17,640 units total streptomycin activity in 63 cc. sputum.

CASE 3. (H. C.). The patient, a sixteen year old white boy, had a history of chronic sinusitis and chronic bronchitis since early childhood. At the age of nine years bilateral permanent antral openings were established without sustained improvement. From the age of fourteen to fifteen years the patient had severe exacerbation of symptoms with increase in sputum to 4 to 6 ounces daily of purulent and mucopurulent material, rarely blood-streaked and slightly foul on one occasion, progressive dyspnea accompanied by asthmatic attacks, and a weight loss of 37 pounds. A week's course of intramuscular penicillin in August, 1944, resulted in no improvement. Residence in Arizona afforded slight temporary improvement until May, 1945, when the patient returned to New York City because of progressive symptoms. Bronchograms

made in the Spring of 1945 were said to show bronchiectasis. A two weeks' course of oral penicillin had no effect.

On admission to the hospital July 20, 1945, the patient appeared acutely and chronically ill, with evidence of marked weight loss. His temperature was 103°F., pulse 110, respirations 26, blood pressure 90/60. Significant physical signs: The nasal septum was deviated to the right with purulent nasal and post-nasal discharge; there were shotty posterior cervical lymph nodes. The chest revealed more prominence of the right side anteriorly with fair bilateral expansion. There were scattered moist coarse and medium râles at the left posterior base and a few inspiratory rhonchi. Extremities showed early clubbing.

Laboratory data revealed the following: Red blood cells 4.7, hemoglobin 13.3 gm., white blood cells 19,600 with polymorphonucleus 85, lymphocytes 8, monocytes 7. Sputum culture: *Staph. albus* predominated. Sinus x-rays: There was marked thickening of the lining membrane of both antra with clouding of the ethmoids. Bronchoscopy revealed left main bronchus suspicious of chronic inflammation. Chest x-rays after lipiodol instillation failed to demonstrate bronchiectasis on the left and the right side

was not visualized. Skin tests showed numerous food sensitivities.

The patient ran a spiking febrile course to 103°F. with occasional chills and profuse sweats for five days, when penicillin therapy was instituted. Sodium penicillin was given intramuscularly, 15,000 units every three hours for a total of 3,010,000 units. Calcium penicillin nasal aerosol with alternating negative pressure was started at the same time, 75,000 units in 3 cc. normal saline five times a day, preceded by praline nose drops, for a total of 8,325,000 units. Within a few days there was marked improvement, temperature ranging around 100°F. and sputum diminishing to 2 ounces of mucopurulent material daily. Dyspnea and wheezing disappeared. The lungs became clear to physical examination. Subsequent sputum cultures showed *B. aerogenes* or *E. coli* predominating. The white blood count was normal. Penicillin blood levels after test mouth inhalation of 50,000 units in 1 cc. normal saline were: 0.1 U/cc. serum at the end of one-half hour; 0.05 U/cc. serum at the end of one hour; 0.01 U/cc. at the end of two hours. The patient gained 10 pounds during his hospital stay of five weeks and had a submucous resection performed toward the end without complications. He was discharged markedly improved.

The patient returned to the hospital seven months later because of increased cough and expectoration, following an acute sinusitis, for another course of nasal penicillin aerosol with alternating negative pressure. At this time the lungs were clear. The patient was ambulatory, afebrile and had gained 25 pounds in the interim. Sputum cultures showed hemolytic staphylococcus aureus predominating. After a total of 2,500,000 units of calcium penicillin aerosol in thirteen days, the patient was discharged from the hospital improved.

He was re-admitted to the hospital August 30, 1946, with a diffuse bilateral bronchopneumonia. (Fig. 7.) Hemolytic staphylococcus aureus was repeatedly cultured from his sputum. Blood cultures were negative. Leukocytosis persisted. Originally, he was on a regimen of intramuscular penicillin, having received a total of 1,000,000 units in one week prior to admis-

sion, with daily dosage gradually being increased from 250,000 units to 2,000,000 units by the end of the first week in the hospital. After nine days in the hospital the dosage was raised to 4,000,000 units daily for ten days by intramuscular injection. During this intensive course of intramuscular penicillin therapy, the patient remained in an oxygen tent, temperature fell from original range of 102 to 105°F. to 100 to 102°F. but tachycardia and dyspnea persisted, respirations ranging between 34 and 50 per minute. Expectoration averaged 8 to 12 ounces daily of yellowish purulent sputum. Hemolytic staphylococcus aureus was found to be resistant to 5 units of penicillin per cc. and 10 units of streptomycin per cc. At this time, nineteen days after admission, chest x-ray revealed only slight clearing. (Fig. 7.) The lungs continued to show numerous coarse and medium moist râles bilaterally with some inspiratory and expiratory rhonchi.

Intramuscular penicillin was discontinued and crystalline sodium penicillin aerosol was started by continuous slow drip into a nebulizer within an oxygen head tent. A daily dosage of 1,000,000 units in 100 cc. normal saline was given over a twenty-four-hour period for seven days. The only additional change in therapy was the use of intravenous aminophyllin 0.24 Gm. daily for three days, and nebulized 1 per cent neosynephrine and Vaponefrin, 0.5 cc. of each three times daily. By the second day of treatment the patient began to show improvement. Bronchodilator drugs were not necessary after the third day, although use of neosynephrine was continued. Bronchoscopy on the fourth day revealed creamy exudate coming from all bronchi which showed edematous reddened mucosa. Culture of aspirated specimen showed *B. coli* only. Daily sputum cultures gradually showed diminution in number of hemolytic staphylococcus aureus colonies and their final disappearance, although the penicillin blood level was only 0.025 U/cc. serum. Gram-negative bacilli predominated on sputum cultures. Temperature ranged between 99 and 100.4°F. Cough decreased markedly and sputum became chiefly mucopurulent in character, measuring 3 to 4 ounces daily, a decrease of over



FIG. 7. Case 3. Admission chest x-ray (left) revealed diffuse bronchopneumonia with major involvement of the right lung and left hilar lymphadenopathy. Chest x-ray (right) eighteen days after admission following massive dosage of intramuscular penicillin revealed very slight improvement.

FIG. 8. Case 3. Chest x-ray (left) one week after penicillin aerosol was substituted for intramuscular penicillin showed moderate clearing. Chest x-ray (right) fourteen days later revealed further clearing of bronchopneumonia, although some enlargement of the left hilar shadow persisted as well as a diffuse bilateral fibrosis and emphysema.

50 per cent. Respirations fell to 28 to 30 per minute. A moderate number of medium moist râles persisted bilaterally posteriorly at the bases. Chest x-ray showed moderate clearing. (Fig. 8.) At the end of this week penicillin aerosol and the oxygen head tent were discontinued. Fifteen per cent sodium sulfacetimide aerosol, 4 cc. five times daily was substituted, using the ordinary mouth inhalation apparatus, for a total of ten days. The patient's respirations were 22 to 24 per minute; temperature remained below 100.2°F. However, hemolytic staphylococ-

cus aureus reappeared on sputum cultures and gram-negative bacilli disappeared. Penicillin aerosol was reinstituted using the mouth inhalation apparatus, dosage of 100,000 units in 2 cc. normal saline four times daily with 1 cc. 15 per cent sodium sulfacetimide added to each inhalation; 30 per cent sulfacetimide was used during the last ten days. This was continued for eighteen days or a total of 7,200,000 units. After the first four days *Staph. aureus* disappeared and gram-negative bacilli predominated on culture. Penicillin levels on arterial and venous blood

taken simultaneously one-half hour after the start of a test inhalation of 50,000 units penicillin showed the same level, 0.2 U/cc. serum. Venous blood levels after test inhalation of 100,000 units were 0.1 and 0.05 U/cc. serum, respectively, at the end of one and two hours. Penicillin levels in the sputum collected for eight hours after a single inhalation of 100,000 units showed 0.2 unit per cc. sputum. Penicillin level in sputum collected by encouraged coughing for ten minutes after a single inhalation of 100,000 units revealed 640 U/cc. sputum. Sensitivity of the hemolytic staphylococcus aureus was reduced to a concentration of 1.6 units per cc. during the course of penicillin aerosol therapy, compared to the original 5 units per cc. during the period of intensive intramuscular therapy.

Temperature remained below 100°F. during the last two weeks of therapy and respirations fell to 20 to 24 per minute. White blood cells fell to 14,650 with a normal differential count. ESR was 37 mm. after one hour. A chest x-ray revealed further clearing but evidence of persisting enlarged hilar shadows and a diffuse fibrosis. (Fig. 8.) The lungs became clear to percussion and auscultation except for occasional post-tussic basal râles. Because of emotional difficulties the patient was discharged improved after a hospital stay of eight weeks to continue penicillin aerosol treatment at home.

CASE 4. (J. K.). The patient, a sixteen year old schoolboy, was admitted to the hospital February 27, 1946, complaining of cough and expectoration for three months, accompanied by intermittent fever, malaise and a weight loss of 8 pounds. He had received a short course of oral sulfadiazine at the onset of his illness with only temporary slight improvement. Sputum amounted to as much as one cupful daily of greenish yellow, purulent, non-foul material. There was a single hemoptysis of one-half cupful bright red blood in the first month, without subsequent streaking. Temperature spiked each day to 101° or 102°F. Sputum was negative for acid-fast bacilli. His past history was unremarkable except for pertussis in childhood and mild, chronic sinusitis for four years.

Examination revealed a well developed, well nourished white boy in no acute distress, but

coughing occasionally. His temperature was 101.2°F., pulse 90, respirations 20, blood pressure 125/70. Positive findings were limited to the chest which showed a slight lag on the right. Over the right lung there was dullness with diminished to absent breath sounds and voice sounds anteriorly and laterally below the level of the fourth anterior rib, with fine and medium moist râles anteriorly near the midline and at the posterior base. The left lung was clear throughout.

Laboratory data revealed the following: Red blood cells 4,750,000, hemoglobin 15.5 Gm., white blood cells 15,800 with 78 per cent polymorphonuclear cells. The sedimentation rate was 57 mm. after one hour; the tuberculin test was negative. Sputum concentrates were negative for acid-fast bacilli. Sputum culture: Staph. albus predominating. Blood culture: No growth in one flask; Staph. albus in the second flask. Chest x-rays (Figs. 9 and 10) revealed consolidation of the right middle lobe and bronchopneumonia in the basal portions of the right and left lower lobes.

Intramuscular penicillin therapy was instituted, 40,000 units every three hours and maintained for three and one-half weeks or a total of 8,000,000 units. Bronchoscopy one week after admission revealed a non-aerating right middle lobe with markedly hyperemic and edematous bronchial mucosa. Thick purulent secretions were aspirated from the right lower lobe, culture of which yielded hemolytic staphylococcus aureus, Strep. viridans and E. coli. The patient ran a low grade fever for two weeks, following which the temperature did not rise above 100°F. Chest x-rays taken on March 11, 1946 (Figs. 9 and 10) showed marked contraction of the right middle lobe but no other change. Sputum had diminished to 10 cc. daily but was still purulent. Accordingly, penicillin aerosol therapy, 50,000 units four times daily was combined with the intramuscular regimen for two weeks, when the latter was stopped and the patient treated with penicillin aerosol alone, dosage being raised to 100,000 units four times daily, using the ordinary mouth inhalation apparatus, preceded by nebulization of neosynephrine and Vaponefrin. At the end of the fourth hospital week and the second week of

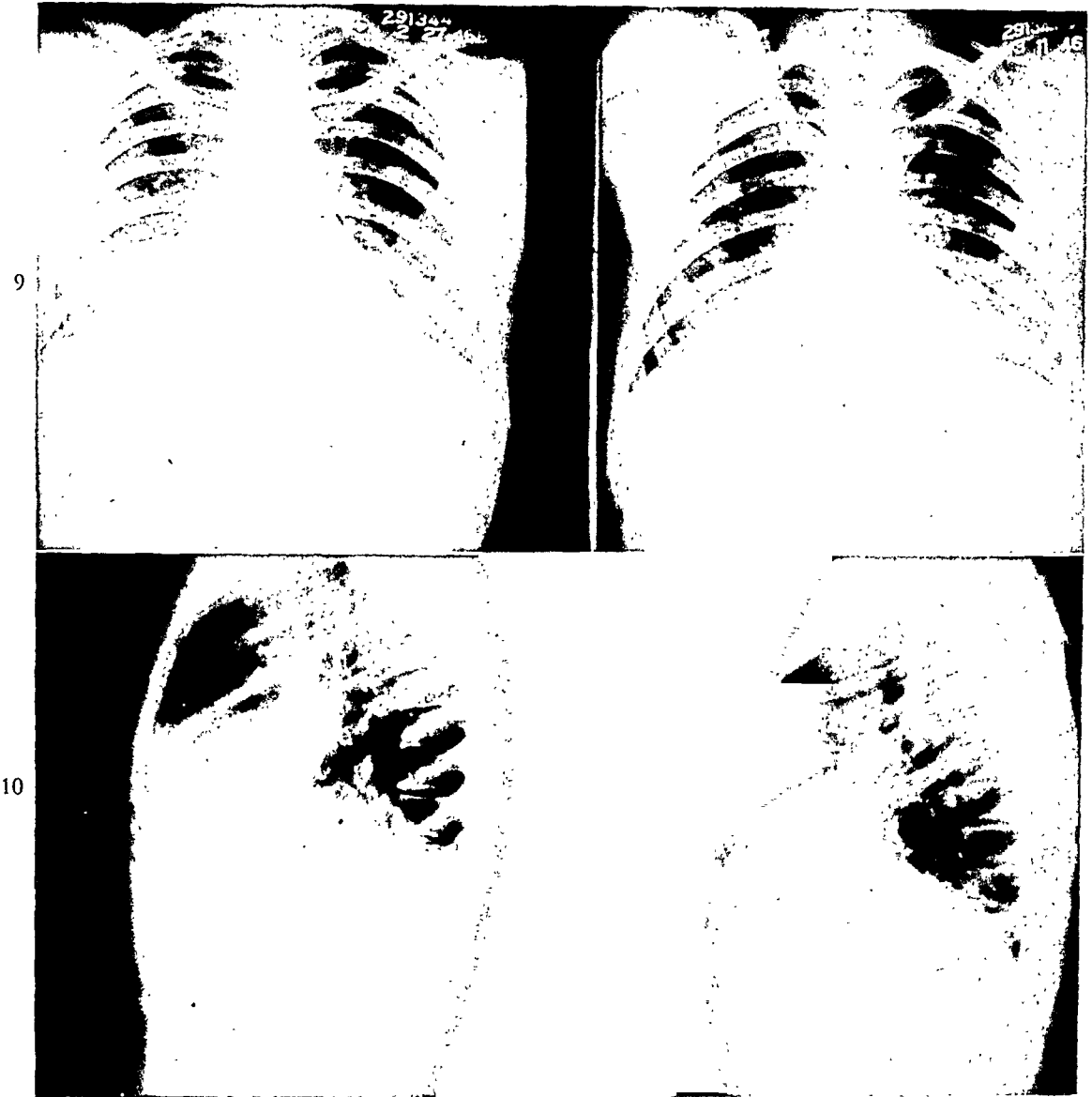


FIG. 9. Case 4. Chest postero-anterior x-ray on admission (left) demonstrating pneumonic consolidation of the right middle lobe and bronchopneumonia of basal portions of both lower lobes, with x-ray appearance (right) after twelve days of intramuscular penicillin showing slight clearing but marked shrinkage of the right middle lobe.

FIG. 10. Case 4. Chest right lateral films on admission (left) and twelve days later (right) revealing marked shrinkage of right middle lobe following initial suppuration.

aerosol therapy, bronchoscopy showed no change in the appearance of the right middle lobe bronchus, and lipiodol instilled through the bronchoscope failed to penetrate the bronchial orifice. No bronchiectasis was demonstrable in the right or left lower lobes. Repeated sputum cultures showed *B. aerogenes* or *E. coli* only.

Because of the clinical improvement and because of the finding of a non-aerated middle

lobe which was the site of a suppurative process, it was decided to defer surgery until an intensive course of penicillin aerosol had been tried using 80 per cent helium 20 per cent oxygen to nebulize the penicillin to obtain better penetration into the right middle lobe by virtue of the lighter gas. Thus far the patient had received a total of 5,200,000 units of penicillin aerosol in three weeks. During the following three and



FIG. 11. Case 4. Bronchograms made two and one-half weeks after substitution of helium-oxygen mixture to nebulize penicillin aerosol show adequate filling of re-expanded right middle lobe without evidence of abscess cavity or bronchiectasis.

one-half weeks a total of 10,000,000 units penicillin aerosol was administered, 100,000 units four times daily nebulized with helium-oxygen mixture, preceded by nebulization of 1 per cent neosynephrine. The patient was ambulatory during this period and asymptomatic. A bronchoscopy two and one-half weeks after this change in regimen showed some opening of the right middle lobe bronchus with decreased hyperemia and edema. Lipiodol now penetrated into the middle lobe and failed to show either an abscess cavity or bronchiectasis. (Fig. 11.) Repeated blood level tests after inhalation of 100,000 units penicillin were negative. One week later penicillin aerosol therapy was cancelled. Physical examination was completely negative. The patient was discharged nine weeks after admission, asymptomatic with a weight gain of 25 pounds, and the follow-up period of eight months has been unremarkable.

COMMENTS

Efficient antibiotic treatment of bronchiectasis, lung abscess and chronic bronchitis requires an adequate local concentration of the drug, which in some cases is not ob-

tained by intramuscular or oral administration. With antibiotic aerosol therapy, administered by appropriate technic effective topical application of the drug may be obtained. In penicillin aerosol therapy an adequate concentration of the drug should be present in the blood as well as in the sputum. However, some patients have shown clinical response to penicillin aerosol therapy without obtaining appreciable blood levels, while others have failed to improve on intramuscular penicillin alone despite high blood levels. An advantage of penicillin over sulfonamide aerosol therapy is that penicillin is not inhibited by para-aminobenzoic acid or purulent exudates. Only traces (0.4 to 0.9 mg. per cent) of sulfacetimide have been found in the blood after inhalation of 2 cc. of 30 per cent sodium sulfacetimide. Para-chlorophenol appears to have a toxicity which militates against its use as an antibiotic aerosol. Sulfamylon is a substance worthy of investigation since it is not affected by the presence of pus, blood or products of tissue necrosis.

It has been used by Howes⁴⁰ in local chemotherapy of wounds with encouraging results. Whether it can be safely given as an aerosol requires investigation.

Sputum cultures of patients treated with penicillin regularly show disappearance of gram-positive penicillin-sensitive organisms. During treatment and for varying periods of time after the termination of treatment, sputum cultures reveal gram-negative organisms, particularly those of the coliform group, predominating. Their pathogenic significance is not clear. However, Abraham and Chain⁴¹ and Woodruff and Foster⁴² demonstrated that these bacteria elaborate an enzyme "penicillinase" which destroys some of the bacteriostatic activity of penicillin. Further investigations are necessary to determine whether patients initially showing a mixed flora in sputum cultures should be started on combined antibiotic therapy, such as penicillin and streptomycin, or changed from one antibiotic to a combination depending on subsequent findings. With the advent of new antibiotics, more suitable combinations may be found, although the problem of development of resistant strains of bacteria must be kept in mind. Advantages of continuous therapy must be weighed against the disadvantages. Sensitivity tests should be checked when feasible at the onset of, during and after therapy, especially when it is prolonged.

Antibiotic aerosol therapy has definite advantages in chronic suppurative pulmonary disease when protracted treatment is required, because of the ease of administration in non-hospitalized patients and in children. The total daily dosage of penicillin aerosol recommended is higher than that required for intramuscular injection, generally being in the range of 150,000 to 500,000 units, although some patients have maintained original improvement on subsequent lower dosage. Relapses are the rule in cases of advanced bronchiectasis if anti-

biotic aerosol therapy is not continued more or less indefinitely. The dangers of inadequate treatment if low dosage or ineffective technic is employed should be kept in mind.

If the tracheobronchial tree is partially obstructed by purulent exudate or congestion and edema of the mucosa, appropriate measures must be taken to insure a patent airway so that antibiotic aerosols may be efficacious. These measures may include bronchoscopic aspiration, postural drainage, and the use of bronchodilator or vasoconstrictor drugs such as aminophyllin or vaponefrin-neosynephrine mixtures by nebulization. If there is considerable obstruction, helium-oxygen mixtures should be tried as the vehicle for antibiotic aerosols.

Systemic reactions to penicillin or to its impurities are less frequently observed with aerosol than with intramuscular administration. Antihistamine drugs such as benadryl or pyribenzamine are useful in relief of allergic reactions.

The incidence of penicillin sensitivity reactions has decreased with the use of the purer crystalline salts. We have encountered no systemic reactions using crystalline penicillin aerosol during the past six months. A few patients have developed local reactions, however, manifested by a coated, black or sore, reddened, smooth tongue. The nature of this reaction is still unknown, although it may be related to some impurities still present or to destruction of some micro-organisms present in the normal mouth flora which are responsible for the usual protective tongue coating. It occurs in susceptible individuals even if the mouth is rinsed well after inhalations. Inhalations may be resumed cautiously after the reaction subsides. The same reaction occurs in susceptible patients given oral penicillin in liquid form, regardless of the dilution. The reaction seems to clear more rapidly if patients are given large

doses of nicotinamide, and sometimes riboflavin. It is possible that the local tongue reaction occurs only in patients with subclinical nicotinamide deficiency, the deficiency subsequently becoming clinically detectable with varying severity. Ellinger and Shattock⁴³ have reported a case of nicotinamide deficiency following oral penicillin. Protective amounts of nicotinamide are being given to patients who previously showed this reaction to ascertain whether it can be prevented in the present course of penicillin treatment. Evidence of increase in irritative cough or bronchospasm with sensation of substernal soreness has been encountered very rarely since the use of crystalline penicillin aerosol. If these symptoms occur, therapy should be discontinued at least temporarily. When resumed, it is generally wise to employ a lower concentration of penicillin.

The importance of the high local penicillin concentration obtained in aerosol therapy has become more clearly manifested in cases with relatively resistant strains, such as the patient with pneumonitis due to *Staphylococcus aureus*. Further studies are in progress to determine the amount and duration of local penicillin activity following inhalations by the various techniques described as an aid in administration of adequate dosage by aerosol therapy. Sputum penicillin levels may ultimately be considered to be as significant as blood levels in the treatment of the groups of bronchopulmonary diseases under consideration.

SUMMARY

Modifications in the technic of administering antibiotic aerosols are described. Penicillin blood levels obtained after inhalation are presented. A large amount of unused penicillin remains in the apparatus. Crystalline penicillin is the preparation of choice, since fewer local or systemic reac-

tions have been encountered with its use. Physiological saline appears to be the most satisfactory diluent for penicillin at the present time.

Attention is directed towards the importance of a high concentration of penicillin in the sputum, as well as an effective blood level, in therapy of suppurative bronchopulmonary disease. Following penicillin aerosol administration, sputum assays reveal high concentrations of the drug, whereas little or no penicillin is found in the sputum after intramuscular injection.

Sputum cultures following courses of therapy with penicillin aerosol show disappearance of penicillin-sensitive gram-positive organisms and predominance of gram-negative bacteria, usually of the *coli-aerogenes* group. Certain sulfonamide aerosols as well as streptomycin may be combined with penicillin in an attempt to eliminate gram-negative as well as gram-positive bacteria from sputum cultures.

Daily dosage of penicillin aerosol employed in treatment of bronchiectasis, lung abscess and chronic bronchitis varies generally from 150,000 to 500,000 units, although in a few instances 1,000,000 units are recommended.

Clinical results of penicillin aerosol therapy in thirty-five patients with bronchiectasis, eight patients with lung abscess and sixteen patients with chronic bronchitis are tabulated, and four case reports with illustrative chest x-rays are presented.

Of fifty-nine courses of therapy in thirty-five patients with bronchiectasis, there was marked improvement in fifteen, moderate in twenty-two, slight in fourteen and none in eight. Of seven courses of therapy in five patients with acute lung abscess, marked improvement occurred in four, slight in two and no improvement in one. Of four courses of therapy in three patients with chronic lung abscess, two resulted in marked improvement, one in

slight improvement and one showed no change. Of twenty-four courses of therapy in sixteen patients with chronic bronchitis, improvement was marked in twelve, moderate in eight, slight in one and absent in three.

Although a final appraisal of the benefit which may be expected from antibiotic aerosol therapy cannot be made at the present time, it is our conclusion that penicillin aerosol therapy constitutes an effective and practical technic which may be added to other forms of therapy in the management of patients with bronchopulmonary suppuration.

The crystalline penicillin was supplied by Commercial Solvents Corporation, the sulfacetimide by Schering Corporation, and the oxygen by the Linde Air Products Company. The nebulizers employed in the investigation were supplied by the Vaponefrin Company. An additional fund was contributed by Mr. Cornelius Crane.

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Portable Unit for Aerosol Medication

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THE benefit of administering various medicaments by the aerosol or inhalation method has been adequately demonstrated by Barach,^{1,1a} Segal,² Vermilye,³ Herrold and Nichols⁴ and others. Among such substances are penicillin, streptomycin and adrenalin. Oxygen, carbon dioxide and oxygen-helium are inhaled directly or used as a vehicle for other substances through a nebulizer. The case,

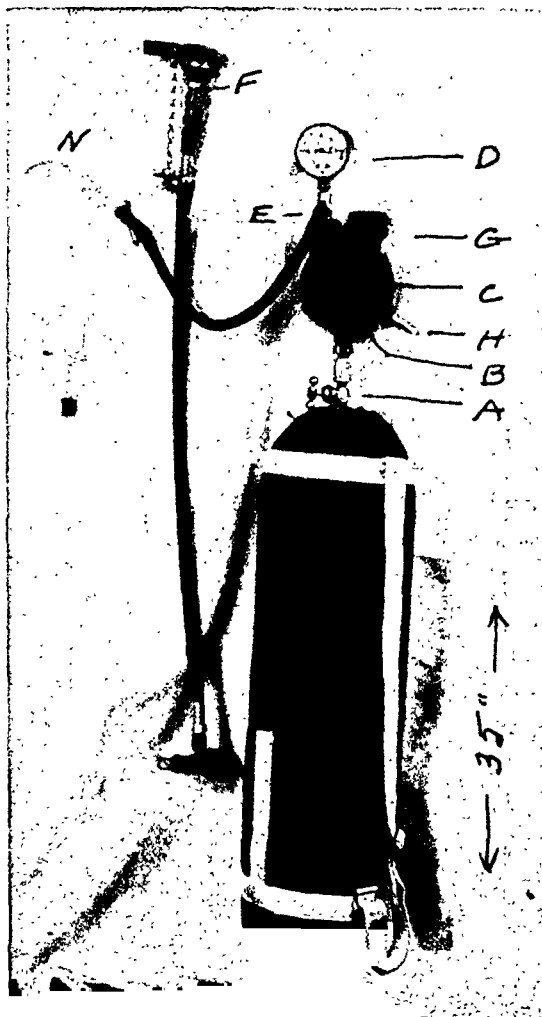


FIG. 1. The unit with case, carrying strap and accessories.

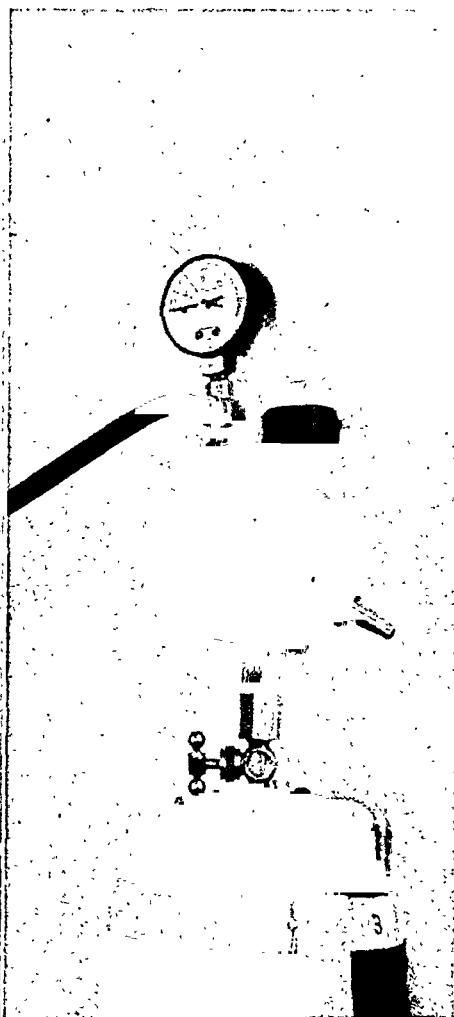


FIG. 2. Enlarged view of the working mechanism.

quately demonstrated by Barach,^{1,1a} Segal,² Vermilye,³ Herrold and Nichols⁴ and others. Among such substances are penicillin, streptomycin and adrenalin. Oxygen, car-

bon dioxide and oxygen-helium are inhaled directly or used as a vehicle for other substances through a nebulizer. The advantages of applying these preparations

directly to local areas are manifest when at the same time a desired blood level is attained by absorption.

The principle drawbacks to the method are the weight and expense of the apparatus and its relative immobility. The large tanks of oxygen require two men and a truck to move them. The pressure gauge and flow-meter cost from \$55.00 to \$75.00 when they are available and are costly to rent. Over one-half of the gas is wasted because of shunting through the open end of a Y-tube, provided for that purpose, during expiration.

The apparatus illustrated overcomes all of these disadvantages. The tank is made of very light weight sheet metal and is encased in heavy duck material with carrying strap attached. It can be lifted or carried with two fingers of one hand, the entire apparatus weighing about 8 pounds. The capacity of the tank is sufficient for about five days' use with four inhalations a day. No oxygen or other gas is wasted. It can be carried easily while walking or riding in autos, trains, planes, buses, ambulances, etc. It can be produced for about one-quarter the cost of the larger apparatus.

Method of Operation. Opening valve A will allow gas to enter chamber B. Finger tip pressure on button C starts a flow through the flow-meter D, outlet E to the nebulizer (N) and into the mouth or through the nasal tubes into the nasal cavity. Release of pressure on C stops the flow. G is a pressure gauge which registers the amount of gas and pressure (to 500 pounds) in the tank. Valve H and cable attachment allow refilling from a large tank in twenty to thirty seconds.

The apparatus fills a distinct need for the administration of medication by the aerosol method in the home or any place where portability, lightness, low cost and ease of administration are desired. This is espe-

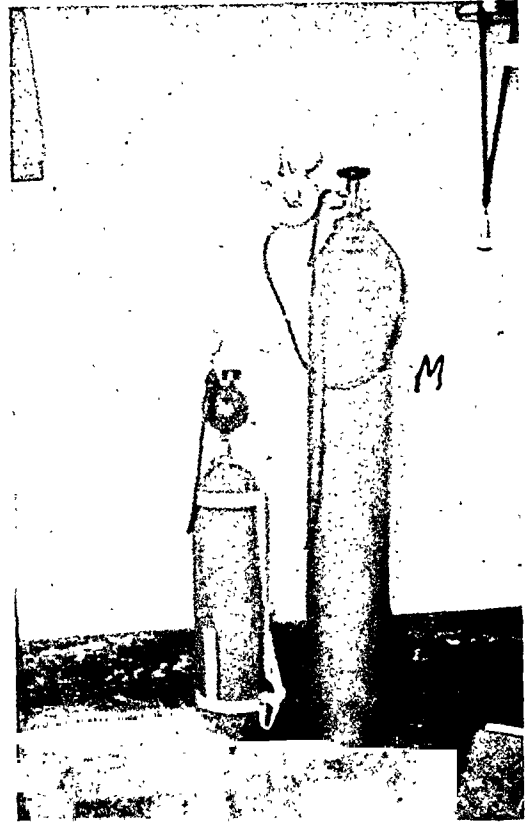


FIG. 3. Size of unit compared to the standard "M" tank of oxygen.

cially true when frequent or painful injections are not possible or well tolerated—also when the medicaments have to be administered over a long period of time in patients not required or able financially to be confined to a hospital.

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567 Fisher Bldg.

Therapeutic and Side Effects of Pyribenzamine and Benadryl*

A Comparative Study Based upon a Survey of Twenty-six Clinical Reports in the Literature

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SINCE the introduction of benadryl early in 1946, and pyribenzamine during October of the same year, some twenty reports on the former and five on the latter drug have appeared in American literature with reference to allergic disorders. By fitting these 3,600 observations into diagnostic groups and adding them to 200 of our own there is adequate material for statistical evaluation of certain of the conditions under consideration. Since eight of the published articles included data on side reactions, it is also possible to draw comparisons between the types and incidence of untoward response with the two agents. This is the dual purpose of the following analysis.

MATERIAL AND METHODS

The various disorders treated with the histamine antagonists have been sorted into the diagnostic groups and subgroups listed in Tables IA and IB which indicate the number of such disturbances observed by each investigator. The general efficiency of the drugs has been appraised by determining what proportion of all trials resulted in improvement (partial or complete). Finally, the various disorders have been arranged in order of their susceptibility to benadryl and

a comparison made with their response to pyribenzamine. (Table III.)

The side reactions have been listed in a similar manner for individual authors, the incidence of each type of side effect being finally estimated on the basis of group averages.

All reports dealt with adult patients with the exception of forty-three cases of Levin, all of Logan's, one of Bowen's, one of Waldbott's and two of Pinkus'. The medication was oral and the dose was usually 50 or 100 mg., repeated after some hours if necessary. For children the amount given was usually adjusted to the weight of the child.

THERAPEUTIC RESULTS

In order to simplify the presentation of therapeutic results Table III will be used as a guide, with occasional reference to detailed Tables IA, IB, IIA and IIB. Although Table III shows that the first four disorders (serum disease, "constitutional" reactions following overdosage with allergens, vasomotor rhinitis due to external, non-seasonal agents and acute urticaria) all yield extremely well to benadryl and pyribenzamine, it is obvious that the first three items cover too few cases for reliable conclusions. Chronic urticaria, hay fever and non-atopic dermatitis of vari-

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TABLE 1A
CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN ALLERGIC DISORDERS: BENADRYL

Investigator	Total Num-ber of Pa-tients	Total Num-ber of Com-plaints	Allergic Rhinitis				Bronchial Asthma				Urticaria		Dermatitis			
			Extrinsic		Intrinsic		Extrinsic		Intrinsic		Acute	Chronic				
			Seasonal	No. Im-proved %	No. Com-plaints	No. Im-proved %	Non-seasonal		No. Com-plaints	No. Im-proved %						
							No. Com-plaints	No. Im-proved %						No. Com-plaints	No. Im-proved %	
			No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %		No. Com-plaints	No. Im-proved %	
Bowen.....	65	65	(...)	20)	18	100	29	73	6	100
Curtis, Owens	18	20	2	50	14	86		
Eyermann....	91	97	52	90	100	36	17	14	93		
Friedlaender																
and Fein-berg.....	83	83	9	78	14	71	13	85
Koelsche.....	83	102	71	71	...	19*	11	2	100	9	67	10	60
Levin.....	223	223	78	59	...	14*	29	1	100		
Logan.....	18	21	12	83	...	2	100	67	...	100	1	100	2	0
Loveless.....	51	53	38	82	100	100	1	0	2	100	1	100		
McElin and Horton....	81	81	22	95	...	8	88	3†	4	100				
O'Leary and Farber.....	236	236	50	92	110	88	25	35
Shaffer.....	13	13	4	100	4	100	3	66
Thacker.....	72	80	70*	46	...	8	50		
Todd.....	188	188	11	100	...	35	100	24*	35	100	43	100	6	33
Waldrott.....	165	165	31	74	...	23	74	47	...	48*	20†	80		
Williams.....	23	23	12*	83				
Gastineau, Harley, Pinkus, Notier and Epstein....	43	43	5	80	11*	9	100	2	100	11	82
Total.....	1453	1493	320	183	23	...	135	...	261	...	76	
Average per cent....	77	...	100	...	60	49	...	39	...	95	...	87	..	58

* Non-seasonal—not specified as to whether intrinsic or extrinsic.
† Not classified as to intrinsic or extrinsic but “mixed” (some infectious).
‡ Urticaria only.

TABLE IB
CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN MISCELLANEOUS DISORDERS: BENADRYL

Investigator	Dermatitis				Dermographism		Physical Allergy		Pruritus		Serum Disease		Migraine		Ménière's Syndrome		Headache		Miscellaneous	
	Contact		Miscellaneous		No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
	No. Improved %	No. Complaints	No. Improved %	No. Complaints																
Bowen.....	5	100	1	100	..	0	..	100	1	100	3	0	1	100	1	0	6	0
Curtis, Owens	2	100	..	0	1	1	0
Eyermann
Friedlaender and Feinberg.....	3	100	1	100	3	100	4	75	1	100
Koelsche.....	3	67	2	50	18	61
Levin.....	1	100	1	0
Logan.....	4	100
Loveless.....
McElin and Horton.....	2	0	2	0	1	100	4	25	6	50	13	69	16	6
O'Leary and Farber.....	38	16	13	85
Shaffer.....	2	50
Thacker.....
Todd.....	5	80	12	83	1	100	8	38	2	100	12	100
Waldrott.....	4	50	3	100
Williams.....	2	100	9	100
Gastineau, Harley, Pinkus, Notier and Epstein.....	4	100	1	100
Total.....	18	..	23	..	6	..	7	..	40	..	3	..	38	..	13	..	14	..	64	..
Average per cent....	..	78	..	74	..	100	..	71	..	20	..	100	..	45	..	69	..	64	..	63

TABLE IIA
CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN ALLERGIC DISORDERS: PYRIBENZAMINE

Investigator	Allergic rhinitis			Bronchial asthma						Urticaria				Dermatitis						
	Total Num-ber of Pati-ents	Extrinsic		Intrinsic		Extrinsic				Intrinsic		Acute			Chronic		Atopic			
		Total Num-ber of Com-plaints	Seasonal	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints	No. Im-proved %	No. Com-plaints		No. Im-proved %					
American Academy of Allergy..	978	978	104	54	11	45
Arbesman ...	495	576	140	85	...	138	72	...	30	48	62	45
Epstein.....	22	22
Friedlaender....	503	503	254	83
Loveless.....	127	151	60	85	...	6	67	...	1	0	8	75
Osborne.....	83	83
Total.....	2208	2313	558	...	144	42	...	70
Average per cent...	78	72	45	...	49

* Not specified as to whether of extrinsic or of intrinsic origin.

† Twenty-seven patients with drug hypersensitivity responded in 89 per cent of the instances; others not hypersensitive to drugs were relieved in 50 per cent of instances.

‡ Eleven patients with drug hypersensitivity responded in 100 per cent of the instances, others not hypersensitive to drugs were relieved in 92 per cent of thirty-six instances.

TABLE III
CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN MISCELLANEOUS DISORDERS: PYRIBENZAMINE

Investigator	Dermatitis		Dermographism		Physical Allergy		Pruritus		Serum Disease		Migraine		Ménière's Syndrome		"Constitutional" Reaction		Headache		Miscellaneous	
	Non-Atopic		No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
American Academy of Allergy...	22	32	23	78	5	40	21	57	6	17	5	20	..	8	5	60	11	27
Arbesman...	6	83	3	100
Epstein...
Feinberg and Friedlaender...	5	80	16	88	3	100	3	33	2	50
Loveless...	1	100	2	50	1	100	17
Osborne...	4	75	2	100
Total.....	31	..	46	..	10	..	26	..	1	..	6	..	5	..	25	..	8	..	13	..
Average per cent....	..	45	..	83	..	70	..	61	..	100	..	17	..	20	50	..	31

ous types responded in over three-fourths of the trials with benadryl. A comparison with the related data for pyribenzamine (PBZ) showed little difference in the efficiency of the two drugs. No comparison was possible, however, in the instance of contact type of eczematous dermatitis since there are no reports on the use of PBZ for this condition. Whereas benadryl benefited the majority of patients with physical allergy, Ménière's syndrome, certain cephalalgias, intrinsic allergic rhinitis and atopic dermatitis, the results were less encouraging with asthma, migraine and pruritus.

The therapeutic results obtained with benadryl and PBZ will now be briefly discussed.

Serum Disease. Four observers each reported symptomatic relief of serum disease in a single patient. (Table III.) The patient given PBZ was in the author's series. She was a young woman who had received a prophylactic inoculation of tetanus antiserum and who developed generalized urticaria within two hours, with subsequent hypotension of critical degree and lapses of consciousness. Once 50 mg. doses of PBZ had been instituted by mouth it was possible to discontinue the frequent injections of epinephrine needed to maintain the arterial tension. The intense pruritus and urticarial eruption were also controlled. After four hourly doses no further treatment was required.

Constitutional Reactions Following Overdosage with Allergenic Solutions. Four cases listed under benadryl and seventeen of the twenty-five patients given PBZ were in the writer's series. The only failures observed were among patients who developed rather marked bronchospasm as part of their "constitutional" response to injected allergen, two of four such patients showing no improvement within thirty minutes after taking 50 mg. of PBZ. All others responded to their accidental overdosage with pollen

extract by developing signs of hay fever, urticaria and occasionally a mild cough or dyspnea. These symptoms and signs yielded uniformly, although not always completely, to one 50 mg. dose of the selected histamine antagonist within twenty or thirty minutes.

TABLE III
DISORDERS ALLEVIATED BY HISTAMINE ANTAGONISTS
IN ORDER OF THEIR SUSCEPTIBILITY TO BENADRYL AND
IN COMPARISON WITH PYRIBENZAMINE

	Benadryl		Pyribenzamine	
	Pa- tients Treated	Num- ber Im- proved, %	Pa- tients Treated	Num- ber Im- proved %
Serum disease	3	100	1	100
Overdose reactions	4	100	25	92
Dermographia	6	100	46	83
Allergic rhinitis, extrinsic non-seasonal	6	100	144	72
Urticaria, acute	135	95	250	85
Urticaria, chronic	261	87	266	79
Dermatitis, contact	18	78		
Rhinitis, seasonal (hay fever)	320	77	558	78
Dermatitis, eczematous and miscellaneous	23	74†	31	45
Physical allergy	7	71	10	70
Ménière's syndrome	13	69†	5	20
Headache, histamine and other types	14	64	8	50
Rhinitis, intrinsic* allergic	183	59	399	58
Dermatitis, atopic	76	58	119	61
Asthma, intrinsic* allergic	210	53†	294	32
Asthma, seasonal	53	49	42	45
Migraine	38	45	6	17
Asthma, non-seasonal extrinsic	23	39	70	49†
Pruritus	40	20	26	61

* Some of the diagnostic data were inadequate to determine whether the patient belonged to the intrinsic or to the non-seasonal extrinsic class.

† Suggested superiority over the other drug.

With the exception of the two patients who required the use of epinephrine, no other therapy was used for the overdose reactions.

The remaining eight trials were carried out by Arbesman in a somewhat different manner. Having noted an untoward response in a given individual after a certain dose of allergen, he then prevented a reaction during the next visit by giving 100 mg. of PBZ twenty minutes beforehand. At the following visit the same amount of therapeutic solution was once more inoculated, with recurrence of the untoward response.

The possibilities of the antihistaminic agents as aids to the management of unduly

sensitive patients and to the shortening of "booster" courses should be more fully explored. Large numbers of observations will be needed in order to minimize the factor of variability in a given patient's handling of a selected dose and to exclude the possibility that the drugs might postpone, rather than avert, the undesirable reaction. It is obvious that the histamine antagonists will prove unsuitable for the relief of serious systemic manifestations if employed by mouth, since too long a time is required for their absorption.

Dermographism. This appears to be a good prospect for therapy with the new drugs. In our single experience both the flare and the wheal with its associated pruritus were decidedly reduced by 50 mg. of PBZ taken twenty minutes before the fingerstroke of the skin. Baer and Sulzberger²⁶ have described a similar experiment. The data on benadryl are few.

Vasomotor Rhinitis, Extrinsic Nonseasonal. An example of this disturbance is the perennial nasal and conjunctival allergic state caused by sensitivity to housedust or animal emanations. The finding that benadryl controlled this type of complaint uniformly, whereas PBZ benefited only three-fourths of the subjects, is no doubt due to inadequate sampling in the former group.

Urticaria. Urticaria was classified as acute if it had been present for three weeks or less. It yielded in a high proportion of some 400 tests with the two drugs. Many of these eruptions had been provoked by chemotherapy, especially with penicillin. The difference noted in the efficiency of the two drugs is probably not of statistical significance, especially since most observers dealt with one agent only. If additional trials indicate that benadryl is superior to PBZ, this may be explained by the greater sedative effect of the former and the well known beneficial influence of sedation upon pruritus.

Chronic urticaria has been thoroughly tested with the two new drugs. The average attack was definitely improved, at least subjectively, by either agent. Considering the therapeutic problems these patients have presented in the past, a positive result in some 80 per cent of all trials is most heartening.

Contact Type of Eczematous Dermatitis. The pruritus, but usually not the lesion of poison ivy and similar eruptions, yielded to benadryl in three-fourths of the eighteen patients treated. Observations on the effect of PBZ are lacking.

Hay Fever. Nearly 80 per cent of the 800 individuals, who were given one or another of the histamine antagonists when they were having seasonal allergic rhinitis, experienced decided relief within half an hour after an oral dose of 50 mg. The agents appear to be of equal efficacy and of real value for this disorder.

Dermatitis, Eczematous and Miscellaneous. That this group covers a heterogeneous assortment of non-atopic eruptions will be apparent from the following facts. The single case listed for Friedlaender and Feinberg in Table IB was described by them as an unclassified dermatitis. The two patients given benadryl by Levin were sulfonamide-sensitive, one of McElin's subjects had psoriasis and another had orthostatic purpura, Shaffer reported one trial with lichen urticatus and another with recurrent dysidrotic eczema, Todd observed twelve patients with eczematoid dermatitis and Pinkus experimented with four individuals who had erythema exudativum multiforme. Seventeen, or 74 per cent, of these patients with heterogeneous disorders responded favorably to benadryl.

The data for PBZ are equally disseminated from the diagnostic viewpoint. The contributors to the report of the American Academy of Allergy listed nine of their trials under the incomplete heading, "eczema,"

five more under the heading, "eczematous dermatitis," seven under "unclassified dermatitis" and one under "drug rash." Of these 22 patients, seven or 32 per cent were improved by pyribenzamine. Feinberg and Friedlaender found that four of their five subjects with unclassified dermatitis were relieved by the drug, as were three of Osborne's four patients with drug eruptions caused by sulfonamides and barbiturates.

It is obvious that more studies will have to be carried out with the various types of non-atopic dermatitis and that more complete information will be needed as to the diagnosis and the degree of relief attained.

Atopic Dermatitis. This was typified by infantile eczema. It was well defined by all observers and an adequate number of patients were involved (nearly 200) to permit of reliable conclusions. Approximately 60 per cent of all trials with either drug brought appreciable relief. However, this was usually of subjective rather than of an objective nature. It will be interesting to learn whether significant sampling of other types of dermatitis will lead to a shift in their positions on the table of susceptibility to the new drugs. The limited data available at this writing place contact and other non-atopic types of dermatitis in the near vicinity of hay fever, an atopic disorder. Atopic dermatitis, on the other hand, falls seven places further down the susceptibility list.

Physical Allergy, Ménière's Syndrome and Headache. Since 70 per cent of trials with the drugs brought more or less relief to patients diagnosed as hypersensitive to cold or heat, it will be profitable to accumulate more experience along this line. The trials with histamine antagonists in Ménière's syndrome are likewise limited in number but encouraging, especially in the instance of benadryl. It will be particularly interesting if the success of the Mayo group with histamine and tension headaches can be

substantiated by additional tests. (McElin, Table IB.)

Intrinsic Allergic Rhinitis. This is a chronic nasal condition characterized by obstruction, watery coryza and sneezing. It is thought to be due to "bacterial allergy" or other inherent factors, rather than to extrinsic allergens which can be determined by a case history and allergic tests. This obscure disorder was responsive, at least partially, in 60 per cent of the 582 trials made with either drug. Since such patients are always therapeutic problems any symptomatic aid will be welcomed.

It should be stated at this point that considerable ambiguity was encountered in the published reports on this group. Indeed, part of the data placed under our heading, "intrinsic" rhinitis may belong under the classification of "extrinsic, nonseasonal" rhinitis. This situation arose because most observers described their patients as having nonseasonal nasal symptoms, without stipulating whether the cause was extrinsic or intrinsic. Transfer of all such data, marked by footnotes in Tables IA and IIA, to the extrinsic column would lower the average for the extrinsic class to 45 per cent in the case of benadryl and to 64 per cent in the instance of PBZ. The figure for the intrinsic groups would conversely be heightened to 90 per cent for benadryl and remain approximately as before for PBZ.

Until future reports clarify the situation, it will probably simplify matters to divide allergic rhinitides into two large classes: the first to contain all cases of known extrinsic origin, whether of seasonal or non-seasonal occurrence, and the second to cover all other varieties. When the data of Tables I and II are combined in this manner, 77 per cent of all trials with either drug for the extrinsic forms gave a positive response. This figure is the same as that found for the seasonal variety alone, which suggests that our classification of doubtful cases (as

intrinsic) was probably correct. It seems probable, therefore, that additional observations upon the intrinsic type will show them to be relatively refractory to the histamine antagonists.

Bronchial Asthma. Bronchial asthma, like vasomotor rhinitis, was difficult to evaluate for the reason that it too was frequently classified incompletely by those experimenting with PBZ and benadryl. Some described their cases merely as those of "asthma" or "non-seasonal asthma," without reference to etiology. These have been indicated by asterisk and footnotes in Tables I and II. They account for 189 of the trials with benadryl listed by us arbitrarily under the heading, "intrinsic asthma" and their removal would leave only twenty-one patients with clearly labelled intrinsic etiology. The latter responded to benadryl in only 29 per cent of the tests. Similar exclusion of doubtful data from the PBZ analysis reduces the number of intrinsic cases to thirteen and the incidence of relief to 31 per cent.

The shift of these doubtful cases into the "extrinsic, non-seasonal" asthmatic class brings the average figure for relief from benadryl up by about 15 per cent (to 54 per cent) and that of the PBZ series down about 15 per cent (to 35 per cent). Our inability to decide in which category the doubtful data belong is perhaps of no great importance, because the result does not differ materially in either analysis from that found for the readily diagnosed seasonal variety of asthma. These extrinsic types were relieved by benadryl in 49 per cent of the trials and by PBZ in 45 per cent. It seems probable that clearly established cases of the intrinsic form will be found even less amenable to antihistaminic agents. At any rate, the present survey indicates that all allergic kinds of asthma yield rather poorly to benadryl and to PBZ, since they will be seen to fall in the lower third of the nineteen disorders named in Table III.

Nevertheless, the need is so great for agents which will relieve asthma without the involvement of the hypodermic syringe or complicated inhalation apparatus that any addition to our armamentarium should be welcomed.

Migraine. Migraine was treated with benadryl by six investigators, with at least partial relief for the patient in 45 per cent of the thirty-eight trials. Only six patients were given PBZ and all but one proved resistant. The possibility that so simple a therapy might be effective for this dreaded complaint makes it urgent that further trials be reported.

Pruritus. Pruritus was little affected by benadryl but rather well controlled by PBZ in a limited experience. O'Leary employed the former for the itching of contact dermatitis, of jaundice, psoriasis, dermatitis herpetiformis and pruritus of neurogenic or toxic origin. No information is available as to the type of patient given PBZ by the American Academy of Allergy group. Further observations will no doubt be forthcoming in the future, since any hope of combatting this most disturbing of conditions ought to be diligently pursued.

Miscellaneous. Encouraging results were reported in limited experiments with such disorders as allergic laryngitis, allergic conjunctivitis, hyperplastic ethmoiditis, overdose reactions and food allergy.

SIDE REACTIONS

Two reports on PBZ and six on benadryl included data on side effects which have been added to our own for analysis of incidence and types.

Table IV shows that 23 per cent of the 1,905 individuals given PBZ developed undesirable reactions. The comparable figure for 655 trials with benadryl was 61 per cent—nearly threefold that of the other drug.

The nature of the side effect and the

TABLE IV
SIDE REACTIONS OF HISTAMINE ANTAGONISTS
(PYRIBENZAMINE AND BENADRYL)

Investigator	Incidence of Side Effects		Distribution of Side Reactions																Total Number of Side Reactions									
	Total Number of Patients Observed	Per Cent with Side Reactions	Drowsiness		Gastro-intestinal		Headache		Vascular		Allergy		Nervous		Numbness of Lips and Tongue		Exhaustion			Dizziness		Muscle Incoordination		Miscellaneous				
			PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %		PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %			
American Academy of Allergy	978	17	..	6	4	..	1	..	0.5	..	0.1	..	2	..	0.7	..	0.1	..	2	0.1	..	168	6
Arbesman*	800	27	..	9	15	..	4	..	2	..	2	..	4	..	2	..	5	6	4	6	0.5	..	376	38
Curtis and Owens	18	17	..	11
Eyermann	52	38	..	25	..	12	21	6	6	..	11
Levin*	223	65	..	38	..	9	8	14	..	3	..	5	9	191
Loveless	127	51	40	71	14	10	2	..	1	..	1	2	4	6	2	2	3	10	6	2	4	1	2	70	52
McElin and Horton	74	73	..	59	..	14	3	22	..	15	8	16	..	4	4	104	70
Thacker	72	67	..	39	..	8	11	..	25	7	..	7
Waldrott	165	56	..	49	..	3	2	0.6	1	92	..
Total	1905	655	..	43	..	8	..	2½	0	..	1	1	3	10	..	6	..	4.6	3	7	0.1	1.4	0.3	614	553	
Average per cent.	..	23	61	8½	9	9	2½	0	1	3	1	1	3	10	..	6	2	4.6	3	7	0.1	1.4	0.3	614	553	..

* Personal communication as well as the published article.

frequency of its appearance are listed for each investigator in Table iv. From this it was possible to list the various manifestations in order of their prevalence with relation to either drug. (Table v.).

The side reaction most commonly en-

TABLE V
SIDE REACTIONS OF BENADRYL AND PYRIBENZAMINE IN
ORDER OF THEIR FREQUENCY

Benadryl		Pyribenzamine	
Side Effect	Incidence %	Side Effect	Incidence %
Sedation.....	43	Gastrointestinal....	9
Central or peripheral nervous system.....	10	Sedation.....	8½
Gastrointestinal....	8	Central or peripheral nervous system.....	3
		Dizziness or vertigo	3
Dizziness or vertigo	7	Headache.....	2½
Numbness of lips and tongue.	6	Exhaustion.....	2
Exhaustion.....	4½	Numbness of lips and tongue.....	1
Vascular.....	3	Vascular.....	1
Muscular pain or incoordination.....	1½	Hypersensitiveness	1
Hypersensitiveness	1	Miscellaneous....	0.3
Miscellaneous....	0.2	Muscular pain or incoordination...	0.1
Headache.....	0		

countered after the administration of benadryl was sedation. It took the form of drowsiness, inability to concentrate, mental confusion, prolonged and untimely sleep, stupor and narcolepsy. These were noted five times more often after the administration of benadryl than following PBZ. Among our own patients the ratio was approximately three to one.

In the instance of PBZ, the most common side effects were in the gastrointestinal tract as evidenced by such complaints as nausea, "bad taste" in the mouth, anorexia, heartburn, epigastric distress, indigestion, abdominal cramps and occasionally vomiting and diarrhea. The second most common

side response to benadryl was one of apparent irritation of the central or peripheral nervous system which led patients to report such states as "wakeful excitement," "jitters," insomnia, irritability, nervous tension, somnambulism, "chills," palpitations, blurring of the vision, diplopia, exuberance, numbness of the extremities, olfactory hallucination (smell of paraldehyde), dryness of the nasal membranes and such urinary disturbances as dysuria, polyuria and frequency. They were encountered in 10 per cent of the trials with benadryl, whereas only 3 per cent of patients given PBZ described such conditions.

Gastrointestinal disturbances were next in order of frequency after the administration of benadryl, being noted in 8 per cent of the patients. Approximately the same proportion of those taking PBZ reported this type of side effect.

Dizziness and vertigo were rather common complications of either drug, being present in 7 per cent of the trials with benadryl and 1 per cent of the PBZ series. Numbness of the lips and tongue occurred in 6 per cent of the tests with benadryl but in only 1 per cent of those with PBZ. It was referable no doubt to local anesthetic action.

Exhaustion (which perhaps should have been included in our sedation class) followed 4½ per cent of the treatments with benadryl and 2 per cent of those with PBZ, ranking sixth in order of frequency for either drug. The next group was comprised of such conditions as flushing of the skin, tachycardia, "tendency to bleed," perspiration, coldness of the extremities, pallor, facial edema, tinnitus and collapse. These were put together under our heading of "vascular." They were present in 3 per cent of those taking benadryl and in 1 per cent of the patients given PBZ.

Such symptoms as tenderness or aching of the muscles, twitchings and impaired

coordination of the extra-orbital muscles were rarely encountered, the incidence being $1\frac{1}{2}$ per cent for benadryl and $\frac{1}{10}$ of 1 per cent for PBZ. The latter was accounted for by two of our patients, one of whom developed diplopia for a short time and another who transiently found great difficulty in lifting small objects for an hour after PBZ had been absorbed.

During the course of therapy, a small percentage (about 1 per cent) of patients given either antihistamine developed what appeared to be hypersensitiveness toward the pill or capsule. For example, the writer observed one individual whose cough was aggravated by PBZ and Arbesman described nineteen who showed an increase in the original complaint during treatment.

Under the heading, "miscellaneous," we included a patient with early menstruation, two instances of impotence, two of menorrhagia and one of emotional depression following the ingestion of PBZ. Only one item was placed in this category for benadryl and it consisted of a feeling of depressed spirits in one of our subjects.

It is interesting that no instance of headache was found among the side effects of benadryl, whereas this was the fifth most common reaction to PBZ, being noted in $2\frac{1}{2}$ per cent of all patients given this drug.

Most of the side reactions discussed above were of mild intensity, requiring no treatment other than discontinuance of antihistaminic therapy. It is the writer's impression that the incidence and severity of side effects can be reduced by the simple precaution of prescribing food or sugar to be taken with the drugs and also by the use of some mild stimulant, such as caffeine or benzedrine, to negate sedation.

SUMMARY AND CONCLUSIONS

This survey of the clinical experience with benadryl and pyribenzamine makes it clear that these drugs confer excellent sympto-

matic relief in urticaria, especially the acute form due to chemotherapeutic agents. Hay fever and other allergic rhinitides of extrinsic (or determinable) origin also yield well, although less spectacularly, to the usual 50 or 100 mg. doses of either drug, whereas cases classed as intrinsic or infectious appear to be less amenable. Atopic dermatitis was improved, at least subjectively, in more than half the reported trials with either drug. Although asthma of all allergic types appears to be less susceptible to the new agents than are other atopic disorders, future observations on well differentiated cases may reveal that a difference exists between the intrinsic and the extrinsic forms as far as their susceptibility to histamine antagonists is concerned.

A number of disorders offer great promise as candidates for this type of symptomatic treatment but observations on them to date are too limited for conclusions. These include serum disease, constitutional reactions due to overdosage with allergenic solutions, dermographism, and to a lesser extent, contact and other types of non-atopic dermatitis, physical allergies, Ménière's syndrome, histamine headache and migraine. Further data should also clarify the usefulness of histamine antagonists in pruritus of various origins.

Side reactions are nearly three times as frequent after benadryl as they are following PBZ. Sedation was noted in 43 per cent of those given benadryl and $8\frac{1}{2}$ per cent of the PBZ group. Whereas this effect was the most common untoward manifestation after benadryl was given, gastrointestinal disturbances ranked first after the administration of PBZ. Other frequently observed side effects with either drug were assumed to be related to central stimulation, since those affected experienced insomnia, nervous tension, restlessness, etc. Dizziness and vertigo held the fourth place for each drug and numbness of the lips and tongue as

well as a sense of generalized exhaustion were relatively common complaints. Infrequently reported, were vascular disturbances (flushing, tachycardia, pallor, etc.), muscular pains and incoördination, headache (occurring only after the administration of pyribenzamine), allergy to the drug and rarely, impotence or disorders of menstruation.

More investigations are needed to determine the sites of action of these new pharmaceutical agents and additional clinical trials are in order to establish their full therapeutic range.

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Evaluation of Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in Bronchial Asthma*

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IN recent years there has been an attempt to produce drugs which would be effective for the relief and prevention of various allergic manifestations. Since it is generally believed that at least some of the symptoms occurring in allergic diseases are due to the liberation of histamine or a histamine-like substance, several chemical compounds have been synthesized in an attempt to block the action of histamine. One of these drugs, dimethylaminoethyl benzhydryl ether hydrochloride, commonly known as benadryl, has been shown to possess high anti-histaminic properties. Animal experimentation has shown that this drug is a powerful antagonist to many of the pharmacological actions of histamine.¹ It was shown to be very effective in relieving anaphylactic shock in guinea pigs and in preventing death from bronchospasm following fatal doses of histamine.²

Clinical reports on the therapeutic effects of benadryl have been favorable when employed in such conditions as urticaria and angioneurotic edema.^{3,4} It seems to be of value in serum sickness and in relieving itching in various types of dermatitis.⁵ When administered orally in sufficient amounts the drug is capable of diminishing the reaction of the skin to histamine.⁶ The reports thus far on its⁷⁻¹⁵ value in bronchial asthma have been inconclusive.

In an effort to determine the value, if any, of benadryl* in the treatment of bronchial asthma, the drug was administered to a group of thirty adult asthmatics who have been attending the Allergy Clinic of the Metropolitan Hospital for many years, and who were resistant to all forms of the usual asthmatic remedies such as elimination of substances giving positive skin reactions, dust and pollen immunization, catarrhal vaccine, and anti-asthmatic drugs commonly employed for symptomatic relief. (Table 1.) The patients' ages ranged from twenty to eighty years and the duration of the asthmatic symptoms was from two to forty years. Twenty-eight of them had complicating organic disease of the sinuses, lungs or heart as demonstrated by x-ray or electrocardiographic examination. Eleven of the patients belonged to the skin negative or infective group, in whom sensitization to specific allergens such as pollens, inhalants and foods was not demonstrated by skin tests or clinical trial. Their symptoms were the result of some infectious process in the paranasal sinuses, lungs or elsewhere in the body. The remainder, or nineteen of the patients, were of the mixed type in that they were skin sensitive and also had chronic

* Generous supplies of benadryl have been made available through the courtesy of Dr. E. A. Sharp, of Parke, Davis & Co., Detroit, Mich.

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TABLE I
CLINICAL DATA IN THIRTY CASES OF BRONCHIAL ASTHMA IN WHICH BENADRYL WAS USED

No.	Case	Age	Duration of Asthma	Type			Frequency of Attacks	Dosage of Benadryl	Clinical Impression			Vital Capacity before and after Benadryl		Side Effects				Complications	Specific Treatment
				All.	Inf.	M.			CR.	I.	U.	Before	After	Drowsiness	Dizziness	Dry Mouth	Fatigue		
1	A. T.	60	8 years		I		Daily	150-300 mg.			U	1.4	1.2	xx	x			Chronic bronchitis with emphysema	D V
2	L. D.	51	12 years			M	Daily	150-300 mg.			U	2.2	1.2	xx	x	xxx		Sinusitis	D V
3	F. R.	48	8 years			M	Daily	150-300 mg.		I		2.3	2.5	xx	xx			Hypothyroidism, obesity	D Thyroid ext.
4	E. O.	75	32 years			M	Seasonal	100-300 mg.		I		2.0	3.0	xx	x			Ragweed pollinosis, pulmonary tuberculosis (healed)	D V
5	J. T.	80	7 years		I		Seasonal	150-300 mg.		I		2.0	2.6	xx			xxx	Generalized arteriosclerosis, parkinsonism	D V
6	J. P.	40	10 years		I		Perennial	150 mg.			U	2.9	3.2	xxx				Sinusitis. Patient refused to continue with benadryl because of severe reactions	D V
7	J. S.	58	12 years		I		Daily	150-300 mg.			U	1.0	1.2	xx	x			Coronary sclerosis, emphysema	V
8	E. P.	57	27 years			M	Daily	150-300 mg.			U	1.4	1.4	xxxx	xx			Patient refused to continue with benadryl because of severe side effects; sinusitis	D V
9	C. W.	54	8 years		I		Seasonal	150-300 mg.		I		1.8	1.6	xx	x			Pulmonary tuberculosis (active?)	D V
10	A. C.	45	25 years			M	Daily	100-200 mg.			U	2.7	2.8	xxx	xxx	xx	xxx	Chronic bronchitis with emphysema; bronchiectasia	KI V
11	A. S.	63	15 years		I		Daily	150-300 mg.			U	1.3	1.2	xx	xx			Discontinued benadryl because of drowsiness; sinusitis	D V KI
12	P. L.	40	6 years				Daily	150-300 mg.			U	1.6	2.3	xxx	xx			Neurodermatitis, sinusitis; discontinued benadryl because of drowsiness	D V
13	T. G.	50	3 years		I		Perennial	150-250 mg.			U			xx	x			Status asthmaticus, pansinusitis	D V
14	J. Z.	29	2 years			M	Seasonal	150-200 mg.			U			xx	x			Arteriosclerotic heart disease, auricular fibrillation, emphysema	KI V
15	D. R.	48	12 years			M	Perennial	150 mg.			U	1.3	2.3	xx	xx			Arteriosclerotic heart disease, auricular fibrillation, emphysema	D V
16	J. P.	68	40 years		I		Perennial	150-200 mg.			U	2.7	2.8			Sinusitis	KI V
17	L. G.	20	9 years			M	Perennial	150-200 mg.		I		1.8	3.0	xx	xx			Arteriosclerotic heart disease, cardiac decompensation, coronary sclerosis	D V
18	R. P.	61	7 years			M	Perennial	150-300 mg.			U	2.2	2.5	xx	xx			Coronary sclerosis, angina pectoris, bundle branch block	KI V
19	N. D.	65	15 years			M	Daily	150-300 mg.			U	1.7	2.1	xxx	xx	x		Chronic bronchitis, typhilitis	D V
20	E. W.	46	35 years			M	Perennial	150-300 mg.			U	3.2	3.4	xx	..			Sinusitis	D KI
21	F. C.	36	8 years			M	Perennial	100-200 mg.		I				x	..			Chronic bronchitis with emphysema; neurodermatitis	D V
22	B. F.	28	10 years		I		Daily	100-300 mg.			U			xxxx	xxxx			Sinusitis; patient discontinued benadryl because of severe side effects	KI
23	B. M.	46	4 years			M	Seasonal	100-150 mg.			U			xxxx	..			Pollinosis, sinusitis, bronchitis	D V
24	J. M.	47	4 years			M	Seasonal	100-200 mg.			U			xxx	xx			Discontinued benadryl because of severe side effects, pansinusitis, emphysema	D V
25	F. G.	42	5 years		I		Daily	150-400 mg.			U			xx	xxxx			Sinusitis, bronchiectasis, pollinosis	T. O. & R. Alt. & Horm.
26	B. R.	21	17 years			M	Perennial	150-400 mg.			U			xxxx	xx			Sinusitis, emphysema, pollinosis	T. O. & R. D V
27	H. W.	27	14 years			M	Perennial	150-400 mg.			U			xxxx	xx			Pollinosis, sinusitis, bronchiectasis. Discontinued benadryl, severe side effects	T. O. & R. D V
28	M. B.	44	11 years			M	Daily	150-400 mg.			U			xx	xxxx			Chronic bronchitis with emphysema; arteriosclerotic heart disease	T. O. & R. D V
29	A. G.	68	2 years		I		Daily	150-400 mg.			U			xxx	xxxx			Pollinosis, sinusitis	D V KI
30	B. E.	47	25 years			M	Perennial	150-200 mg.		I				xx	xx				T. O. & R.

All.—Allergic
Inf.—Infantile
M.—Mixed
CR.—Complete Relief

I—Improved
U—Unimproved
Spirometer studies were done with a Collins Spirometer and measurements were made in liters per square meter of body surface

D—Dust extract
V—Vaccine
KI—Potassium iodide
T.—Timothy grass pollen
O.—Orchard grass pollen
R.—Ragweed pollen
Alt.—Alternaria
Horm.—Hormodendron

infections. None of the patients could be classified as solely of the skin sensitive type.

All of the patients were at first given 150 mg. of benadryl daily. They were instructed to take 1 tablet (50 mg.) by mouth three times a day after meals. When no relief was obtained after two week's trial, the quantity was gradually increased in an effort to determine the patient's daily requirements. An additional 100 mg. was prescribed at bedtime. If no improvement followed, the dosage was increased further to 300 to 400 mg. per day (100 mg. three times a day after meals and sometimes an additional 100 mg. at bedtime). The patients were observed for a period of six months and were required to keep daily records of their symptoms. Once a week the results were recorded as symptoms completely relieved, improved or unimproved. When the improvement persisted for a period of four weeks on benadryl medication a placebo was substituted for a period of two weeks. Immunization treatment with pollen extract, dust extract or catarrhal vaccine was continued. All anti-asthmatic drugs except benadryl were discontinued but when benadryl was shown to be ineffective such medications as ephedrine, potassium iodide or aminophyllin were used in conjunction with benadryl. Pulse studies were made on all of the patients. Spirometer determinations were made on eighteen patients before and after taking benadryl using the Collins respirometer; measurements are recorded in liters per square meter of body surface.

RESULTS OF TREATMENT

Seven of thirty patients or 23 per cent treated with benadryl reported symptomatic relief. It is of interest to note that these patients showed no evidence of organic lung or heart disease except Case 4 whose x-ray revealed some healed tuberculous scars. Furthermore, episodes of acute respiratory infections were conspicuously absent in

these patients during the six-month period of observation. Two of these patients (Cases 5 and 9) belonged to the skin negative or infective group. In these two patients it was difficult to evaluate the benefit obtained because they had mild wheezing and cough

TABLE II
COMPLICATING PATHOLOGICAL CONDITIONS PRESENT IN
TWENTY-THREE ASTHMATIC PATIENTS UNRELIEVED
BY BENADRYL.

Pathological Conditions	No. of Patients
Sinusitis	8
Sinusitis	2
Bronchitis	
Sinusitis	1
Bronchiectasis	
Sinusitis	2
Emphysema	
Chronic bronchitis	2
Emphysema	
Chronic bronchitis	1
Emphysema	
Bronchiectasis	1
Chronic bronchitis	
Emphysema	1
Arteriosclerotic heart disease	
Chronic bronchitis	1
Syphilis	
Pulmonary tuberculosis	1
Emphysema	1
Coronary sclerosis	
Arteriosclerotic heart disease	1
Auricular fibrillation	
Emphysema	1
Arteriosclerotic heart disease	
Cardiac decompensation	1
Coronary sclerosis	
Coronary sclerosis	1
Bundle branch block	

only during extremes of temperature. Moreover, when a placebo was given them similar relief was reported. The other five patients belonged to the mixed group (allergic and infective—Cases 3, 4, 17, 21 and 30). They received the usual allergic management in conjunction with benadryl.

CASE 3. A female, age forty-eight, had slight wheezing daily for the past eight years. She took thyroid extract for hypothyroidism and obesity. She was highly emotional. Her symptoms lessened for eight weeks on an intake of 150 mg. of benadryl per day. When she was given a placebo for two weeks her symptoms became worse. When she took 300 mg. of benadryl a day she had complete relief.

CASE 4. A male, age seventy-five, had mild asthma for the past thirty-two years. X-ray examination of his lungs showed healed pulmonary tuberculous lesions. His asthmatic symptoms occurred during extremes of temperature and during the hay fever season. When given 150 mg. of benadryl per day there was no improvement. When benadryl was increased to 300 mg. per day he became symptom-free. When a placebo was substituted for the benadryl the asthmatic attacks recurred.

CASE 17. A female, age twenty, had daily asthma for the past nine years. Prior to treatment with benadryl she suffered from severe asthma as the result of an acute sinus infection. She required intravenous aminophyllin for relief. When the sinus condition improved she was given 150 mg. of benadryl daily and reported that there was a marked improvement in her asthmatic condition. When a placebo was substituted for the benadryl her condition remained the same. She had no further sinusitis while under observation.

CASE 21. A female, age 26, had asthma for the past eight years. Intracutaneous tests showed her to be markedly sensitive to house dust and animal danders. She was subject to occasional attacks of sinusitis and was highly emotional. Her asthmatic attacks became milder on an intake of 300 mg. of benadryl daily. The substitution of a placebo was followed by a recurrence of her asthma. She has had no sinusitis while under observation.

CASE 30. A female, age forty-seven, had asthma for twenty-five years. During the summer months her asthma occurred in association with early and late hay fever symptoms. During the winter months she had frequent acute sinus infections which were accompanied by chest symptoms. When given 150 mg. of benadryl a day her nasal and chest symptoms were greatly decreased in severity. The nose and chest symptoms at this time were the result of pollinosis. When she took 100 mg. of benadryl at bedtime her symptoms diminished sufficiently to insure a good night's sleep.

Twenty-three of the thirty patients or 77 per cent treated with benadryl failed to obtain any relief whatsoever. All of them

showed organic changes in the lungs or heart or an active sinus infection. (Table II.) In some cases the drug seemed to aggravate the asthmatic symptoms but it was deliberately increased with no relief. When benadryl was used in conjunction with other anti-asthmatic drugs such as ephedrine, potassium iodide or aminophyllin the relief obtained was greater than when the latter drugs were used alone. Benadryl was found to be especially helpful when administered in 100 mg. doses at bedtime. Such a procedure usually insured restful sleep.

A slight fall in blood pressure was noted in twenty-two of the thirty patients following the administration of 50 and 100 mg. doses of benadryl. No significant changes in vital capacity followed the use of this drug.

SIDE REACTIONS

The majority of the patients, twenty-eight or 93 per cent, complained of ill effects while using benadryl. Drowsiness occurred in all twenty-eight, dizziness in twenty-three, dry mouth in three and fatigue in two of the patients. Six patients refused to continue the drug because of these untoward reactions (Cases 6, 13, 14, 23, 25 and 28). These symptoms disappeared when the drug was discontinued and reappeared when again used. In three of these patients (Cases 13, 14 and 23) the side reactions were so severe as to warrant discontinuance of the drug at an earlier date but they were prevailed upon to continue it in order to note any tendency to overcome such reactions.

COMMENTS

Benadryl has been shown to possess high anti-histaminic properties in animal experimentation. Clinically the drug demonstrates a pronounced action on the allergic wheal. It diminishes the reaction of the skin to histamine and has proven of value in the treatment of such conditions as urticaria,

angioneurotic edema and serum sickness and in relieving the itching of various types of dermatitis. The reports on the therapeutic value of benadryl in bronchial asthma have not been definitely established.

To evaluate the effect of this drug on the symptoms of bronchial asthma it was administered to thirty adults who had experienced asthmatic attacks for many years with little relief from the usual asthmatic remedies. The majority of the patients were middle aged or elderly individuals with advanced stages of bronchial asthma and with organic disease of the lungs, heart or paranasal sinuses. There were no infants or children in this group.

Benadryl, administered in dosages of 150 to 400 mg. daily, produced symptomatic relief in 23 per cent of the patients. This improvement was only temporary and palliative. When the drug was of help, 50 to 100 mg. controlled the cough and wheezing for from four to eight hours. These patients had no complicating conditions in the lungs or heart, and their asthmatic symptoms could not be attributed to acute respiratory infections. When the asthmatic symptoms occurred as a result of nasal allergy especially pollinosis, benadryl relieved the nasal symptoms and lessened the severity of the chest symptoms.

Seventy-seven per cent of the patients obtained no relief whatsoever while using benadryl alone. All of them showed either organic lung or heart disorders or acute infections in the paranasal sinuses. However, when the drug was prescribed in conjunction with other anti-asthmatic remedies such as ephedrine, potassium iodide or aminophyllin it proved of further help in relieving the symptoms.

Benadryl seems to be of limited therapeutic value in controlling the symptoms of bronchial asthma. The drug was ineffective when the asthma was precipitated or complicated by respiratory infections, especially

acute sinusitis, or when organic changes of the lungs or heart were present. Severe asthmatic episodes were uninfluenced by benadryl administered orally regardless of the etiology. The blood pressure was slightly lowered in twenty-two of the thirty patients and the spirometer readings remained unchanged following use of the drug. The side reactions of the drug in producing drowsiness, dizziness and other ill effects obviated its continued use for long periods of time. The edema and spasm of the bronchial musculature producing the asthmatic symptoms cannot be explained solely on the basis of the liberation of histamine. Other physiologic changes are probably involved. However, there is enough hope in drugs of this nature to warrant further experimentation for a substance with greater therapeutic value and better tolerance. Such a compound has been synthesized and clinical studies are now in progress.

SUMMARY

1. Benadryl was administered orally in dosages of 150 to 400 mg. daily to a group of thirty adult asthmatics who were resistant to all forms of the usual asthmatic remedies.

2. Seven or 23 per cent of the patients experienced symptomatic relief. Withdrawal of the drug was followed by recurrence of symptoms.

3. Benadryl was beneficial to those patients whose asthmatic symptoms were not due to acute upper respiratory infections or to demonstrable organic lesions in the lungs or heart.

4. Twenty-three or 77 per cent of the patients failed to obtain any relief whatsoever. All of them showed organic changes in the lungs or heart or an active sinus infection.

5. The drug was without immediate effect upon severe attacks of asthma, regardless of etiology.

6. Benadryl was found to be helpful when

used in conjunction with known anti-asthmatic drugs.

7. Side reactions such as drowsiness, dizziness, dry mouth and fatigue occurred in twenty-eight or 93 per cent of the patients.

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Diagnosis of Brill's Disease (American Form of European Typhus Fever) by Skin Biopsy*

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EPIDEMICS of classical typhus fever have broken out periodically in Central Europe for many hundreds of years and in the United States as late as the nineteenth century. The etiological agent was established by the brilliant work of Howard Taylor Ricketts in 1910 and the organism now bears his name. At present several varieties of the rickettsial diseases are found in the United States. Because of recent advances in treatment, both with immune serum and with para-aminobenzoic acid, early diagnosis is of extreme importance since present treatment, to be effective, must be started within the first week of the disease. We present here a simple practical procedure for the early diagnosis of the rickettsial diseases.

In 1910, Brill¹ published a series of cases which strongly resembled epidemic (classical or European) typhus fever. Most of Brill's patients with the disease had immigrated here from the typhus regions of Europe. It was therefore not clear whether the disease represented classical typhus (either as an importation from Europe or as a recurrence of latent infection) or was of local origin, possibly flea-borne. Several years later a somewhat similar typhus-like disease was described in Georgia² and since then thousands of cases have been reported, particularly from the Southeastern section of the United States. The term "Brill's disease" was at first applied to these cases; however, it soon became evident that the typhus fever seen in the Southeastern part

of the country differed from the disease described by Brill.

The confusion surrounding the rickettsial diseases led many³⁻⁵ to believe that both Brill's disease and Southeastern (murine) typhus were solely of native origin. In 1934, Zinsser⁶ represented Brill's disease as a recrudescence of an old attack of typhus fever. Plotz⁷ subsequently demonstrated the immunological identity of Brill's disease with classical typhus, separating it from the endemic (murine) form of typhus. Using the complement fixation technic in twenty-three cases of Brill's disease, Plotz found that the pattern of fixation in this disease resembled that obtained in epidemic typhus fever. His studies indicated that mild cases of epidemic typhus actually exist in the United States in a sporadic form. Apparently one attack of typhus does not confer a lifelong immunity as was generally believed. The virus may be harbored in the body and with lowering of the resistance of the host the virus may multiply and induce a mild attack of the disease. Man may serve as a reservoir for epidemic typhus between outbreaks of the disease just as the rat does in endemic typhus.

It is probable that many of the cases previously reported in the Northeastern United States as Brill's disease and which occurred in native Americans would now be classified as Rocky Mountain spotted fever; laboratory data necessary for accurate differentiation of the typhus-like fevers were lacking at the time these reports were made.

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In fact, of three cases reported by Flippin,⁸ the author admits that two probably represented cases of Rocky Mountain spotted fever; one had given a definite history of tick bite.

These earlier attempts to classify the rickettsial diseases occurring in the United States resulted in much confusion. The same disease has been described under different names and the same terminology has been applied to separate disease entities. At present there seem to be three distinct types of rickettsial disease in this country. It now seems advisable to classify them as first, the *American form of European typhus fever*, which represents Brill's disease and occurs in the northeastern part of the country; second, *murine typhus*, which has the rat flea as a vector and is endemic to the southeastern part of the country, and third, *Rocky Mountain spotted fever*, with ticks as the vectors and occurring throughout the United States.

The etiological organism is a small polymorphous micro-organism, the *Derma-centroxenus rickettsia*; *R. prowazeki* is responsible for the classical form of typhus fever; *R. mooseri*, for the murine type and *R. rickettsii* for Rocky Mountain spotted fever. Both Plotz⁹ and Felix¹⁰ have demonstrated that the morphological variations in the different types of rickettsiae are not to be regarded as indicating specific morphological differences. Since they are so strikingly similar in appearance (excepting the organism responsible for tick-borne Q fever), the following description is applicable to all types seen in the United States.

The organism stains best with Giemsa stain and other special stains. When stained with Giemsa stain in the usual fashion¹¹ they appear to be larger and more distinct. Early, Pinkerton³ described the rod forms of the organism and thought that the cocci seen were paired rods seen standing on end. They appeared as minute diplobacilli, 1.2

by 0.3 microns to 1.6 by 0.3 microns. The organism is non-filterable and appears as short and long chains, occasionally as a filamentous form. Using Giemsa stain, Sikora¹² clarified the description of the various forms of the organism showing how each type corresponded to a different stage in growth and development. These included (1) round or oval non-cellular granular forms, each of which elongates to form (2) a short, rod-shaped or barrel-shaped cellular body with a granule at each end which further elongates and subdivides into (3) a bacilliform body containing three or four granules in each. Each bacilliform body then divides into (4) two plump bodies, each of which has two polar granules which elongate and become (5) dumb-bell shaped. More recent studies of the Rickettsiae with the aid of the electron microscope^{9,13} show them to be pleomorphic, with both rod-like and coccoid forms. The bacillary forms are seen to have a limiting membrane enclosing a substance which is moderately opaque to electrons; in some cases spherical granules are seen within the organism. Some forms are completely opaque while others are transparent. The smaller coccoid forms, which cannot be distinguished with certainty from tissue particles by ordinary methods, have the same structural appearance as the bacillary forms. These studies apparently confirm the belief that the Rickettsiae occupy a position intermediate between bacteria and the filterable viruses.

The essential pathologic changes in all rickettsioses are similar with minor variations which will be described. Frankel¹⁴ in 1914 described the histological appearance of the lesions in classical typhus fever. The changes are an expression of intrinsic vascular, usually intimal, damage due to the multiplication of the Rickettsiae in the lining of the endothelial cells or in the smooth muscle cells of the blood vessels.

The extent of the damage depends upon the character and virulence of the particular rickettsial infection. The presence of these organisms¹⁵ causes swelling and proliferation of the endothelium, cellular infiltration of the vessel walls, perivascular accumulation of mononuclear cells and occasionally thrombosis and hemorrhage. The vessels appear to be enclosed by a sheath of infiltration. These vascular changes are of the same general type throughout the body and usually affect the smaller vessels of the skin, brain, lungs and heart. The proliferative endangiitis involves the arterioles, capillaries and at times the venules; occasionally the larger vessels are also involved. In classical typhus this swelling and proliferation of the infected endothelial cells in the small vessels causes occlusion more frequently than in mite typhus fever.

The skin is one of the chief organs in which these characteristic vascular changes occur and the skin macules show inflammatory involvement of the small blood vessels with endothelial proliferation. The perivascular infiltration¹⁶ consists chiefly of lymphocytes with a few polymorphonuclear cells. Escape of blood from the damaged vessels is the basis of the petechiae. The accumulations of mononuclear cells form small nodular lesions; these are characteristic and are seen more commonly in the skin and brain. In classical typhus fever¹⁷ the capillary thrombi, while not constantly present, are more conspicuous when they do occur and the endothelial cells are more obviously damaged. There is also a tendency to a necrotizing arteritis which is not found in the mite form of typhus fever. The macules in Rocky Mountain spotted fever^{17,18} resemble those of classical typhus. Here, also, Lillie¹⁹ has shown numerous perivascular foci of lymphocytic infiltration with swelling of the capillary endothelium and concentric proliferation in the skin. Throm-

boses of the arterioles and venules were uncommon.

Rickettsiae have frequently been demonstrated in the cytoplasm of the endothelial cells of the vascular lesions. Pinkerton^{3,20} described their appearance in the vessels of the brain and skin. Lillie¹⁹ noticed that they were easily found in many of his cases.

CLINICAL PICTURE OF BRILL'S DISEASE

The onset is abrupt and a shaking chill is not uncommon. Headache, backache and pyrexia are prominent. The headache is excruciating and usually is not relieved by the common remedies; resort to spinal tap may bring appreciable alleviation. Backache and generalized muscular aching are troublesome. Malaise and gastrointestinal symptoms are common. The fever rises rapidly, is continuous and unremitting and falls by crisis or lysis about the tenth or twelfth day. The conjunctivae are injected, occasionally accompanied by photophobia and lacrimation. Some nuchal rigidity is evidenced. Drenching sweats, tinnitus and deafness are common. Early prostration is characteristic of the disease in contrast to the first week of typhoid fever. It resembles more closely the exhaustion of the third week of typhoid fever.

The rash usually appears on the fourth day; its appearance is rarely delayed as late as the seventh day. A constant succession of lesions occurs; first over the anterior axillary folds and sides of the abdomen and then it spreads peripherally to involve gradually the chest, back, shoulders and extremities in that order. It may involve the dorsum of the foot and the back of the hands. As a rule, it spares the palms of the hands, the face and the neck. It rarely itches. The lesions appear as irregular, round or oval elevated areas of macular eruption, 1 to 5 mm. in diameter, pink to bright red, disappearing on pressure except when they become hemorrhagic. Rarely, the lesions

may become necrotic. Characteristic of the rash is its irregular distribution, the depth of color and its outline.

The nervous symptoms parallel the degree of central nervous system involvement. A non-productive cough occurs in about half the patients. Pneumonia is not uncommon and may protract the course.

The mortality rate of Brill's disease rarely exceeds 1 to 2 per cent. Fatalities are usually confined to the encephalitic forms and to older patients with accompanying myocardial or renal complications. This compares with a mortality rate of 6.1 per cent in 2,233 patients with murine typhus²¹ reported during 1938.

Diagnosis. Weil and Felix²² first described an agglutination test giving a response with *Proteus* organisms, OX 19 strain. It is significant if elevated above a 1 to 80 dilution. Stuart and Pullen²³ reported that in 180 cases of murine typhus fever no test was positive before the fifth day. In this series ninety-five tests failed to reveal the presence of agglutinin; the average time after onset when these tests were made was 6.8 days. The average time required for the appearance of agglutination titers of 1 to 80 was 8.5 days; 1 to 160, 10.5 days; 1 to 320, 11.4 days; 1 to 640, 13.3 days and 1 to 1,280, 15.9 days.

The proteus reactions do not differentiate between louse-borne typhus, Brill's disease and murine typhus.¹⁰ In Rocky Mountain spotted fever the reaction is highly irregular. The complement fixation technic described by Plotz²⁴ has proved adequate for serological separation of the rickettsial agent of endemic typhus, Q fever and Rocky Mountain spotted fever but it was of no help in differentiating between epidemic and endemic typhus fever. With the use of prepared rickettsial antigens⁷ epidemic and endemic typhus fever can be differentiated. Van Roogen and Bearcraft²⁵ reported on the use of specific agglutination tests

against *Rickettsia*. In seventy-two cases of typhus fever there was correlation between the Weil-Felix reaction and the rickettsial agglutination test. Both tests, however, are seldom positive before the seventh day of the illness, two to three days after the appearance of the rash. The rickettsial agglutination test reactions are maximum about the fourteenth day of the illness and may persist for as long as two years, as compared with the proteus agglutination which fades rapidly.

So pathognomonic of typhus fever is the pathological picture of the lesions in the arterioles and capillaries that biopsy of these was suggested as a diagnostic procedure as far back as 1914,¹⁴ and more recently by Pinkerton.²⁰ However, to our knowledge this procedure has never been adapted as a diagnostic aid.

The clinical pattern presented in patients with suspected rickettsial disease challenges proper interpretation even after appearance of the rash. The serological tests are seldom of help until the third or fifth day, or longer, after the appearance of the eruption. It is well known that a large percentage of cases will give a negative response to the Weil-Felix reaction. Many hospital laboratories are not equipped to perform the newer rickettsial complement fixation and agglutination tests; therefore, we suggest this practical and simple method for the early diagnosis of rickettsial fevers.

A well developed lesion, preferably of a macular type, is excised with ample underlying tissue. It is fixed in Regaud's fluid and stained using the usual Giemsa method. An experienced pathologist can easily recognize the characteristic lesions even in the absence of the rickettsial bodies. In classical typhus, Brill's disease and murine typhus the *Rickettsiae* may be found in the endothelial cells lining the blood vessels. Even in the absence of the organism the proliferative endangiitis is diagnostic. In Rocky Mountain spotted

fever the *Rickettsiae* rarely will be seen in the smoother muscle cells of the arterial walls.²⁰

CASE REPORTS

CASE I. A thirty-nine year old white female was admitted to the Jewish Hospital of Brooklyn complaining of fever, headache, vomiting and generalized body aching for a duration of four days. She was born in Poland and had been a resident of the United States for the past twenty-six years. At the age of five she had contracted typhus fever during the European epidemic of the first World War. The remainder of her past history and family history was irrelevant.

Four days before admission to the hospital she became ill with a fever of 105°F. This was accompanied by severe frontal headache, generalized aching and nausea. A shaking chill was present every morning. The fever continued remittent, reaching a peak at 3 P.M. and again at 1 A.M., never returning to normal. It was accompanied by marked sweating. For the two days preceding admission there had been constant vomiting; diarrhea, with loose, watery stools was present the day before admission.

Physical examination showed a well developed, well nourished white female who appeared acutely ill. The temperature was 103°F. with a pulse rate of 100 per minute. The face was flushed and the patient exhibited marked photophobia and hyperesthesia. The eyes had a feverish, glassy appearance. There were several pinkish macular areas over the abdomen which faded on pressure. The remainder of the physical examination was normal with the exception of an enlargement of the spleen which was felt two fingers below the costal margin.

A spinal tap performed on admission showed 68 cells per cu. mm. These were predominantly lymphocytes. There was a slight trace of protein. Sugar and culture of the spinal fluid were negative. Another spinal tap repeated on the third hospital day showed a clear fluid without cells. Routine studies on this fluid were negative.

The macular rash became more prominent on the second hospital day but still continued to fade upon pressure. It had now spread over the chest and back as well as the abdomen, and



FIG. 1. Section of skin macule. Blood vessels within corium are distended. There is proliferation of the endothelium. The blood vessels are surrounded by a collar of inflammatory cells which consist of polymorphonuclear leukocytes and small and large mononuclear cells; hematoxylin and eosin stain $\times 600$.

some of the macules did not blanch with pressure. The rash began to fade on the fourth day until it was barely visible on the eleventh hospital day.

During the first week of hospitalization the patient had an intermittent fever ranging from 100.2°F. to 103.4°F. Penicillin, 50,000 units every three hours, was given intramuscularly for the first week without apparent effect. The temperature fell by lysis and reached normal on the ninth hospital day (the thirteenth day of the illness). At this time the spleen was barely palpable. Convalescence was uneventful and the patient was discharged on the seventeenth hospital day.

The laboratory studies showed several urine examinations to be normal. A slight secondary anemia was present with a leukocyte count of 3,550 and a normal differential count. The leukocyte count rose progressively during the illness until it reached 8,450. The sedimentation



FIG. 2. A, section of skin macule. The blood vessels of the upper part of the corium show swelling of the endothelial cells and granular degeneration of the cytoplasm. The swollen cells are filled with minute, bluish-black coccoid bodies in clumps within the cytoplasm; Giemsa stain $\times 2255$.

rate was 25 mm. (Westergren) in one hour. The Kline test was negative. Many blood and stool cultures were negative. Repeated agglutination studies for typhoid, paratyphoid, tularemia and brucella were negative. The heterophile agglutination titer was 1 to 8 and later 1 to 32. *Proteus* OX 2 and 19 agglutination reactions taken on the sixth hospital day were negative.

A skin biopsy of a macular lesion from the abdomen was taken on the third hospital day. Microscopic examination (Fig. 1) showed distended blood vessels within the corium, the endothelium of which was somewhat swollen. Surrounding some of these were collars of inflammatory cells. The cells included polymorphonuclear leukocytes as well as small and large mononuclear cells. With Giemsa stain some areas showing dark coccoid bodies were seen but they could not be definitely identified as rickettsiae. The pathological picture showed a toxic vascular disease that was compatible with that seen in typhus fever.

CASE II. A thirty-four year-old white truck driver was admitted to the Jewish Hospital after eight days of fever. He was Russian-born and had been in the United States for the past twenty-four years. As a child in Russia he had had a severe febrile disease accompanied with pneumonia. There was no other recollection of illness previous to this admission.

His illness began on the eighth day before admission with severe frontal headache which was aggravated on bending forward and which lasted for two days. That night he noted a fever of 102°F . The persistence of the fever led him to call a physician two days later. In spite of oral penicillin and antipyretics every three hours the fever continued intermittently, with daily rises as high as 105°F . in the morning and evening and down to 101°F . during the afternoon. During this period the frontal headache reappeared and was severe enough to prevent him from sleeping. There was no pain on movement of the eyeball. Another physician who saw the patient the day before admission placed him on sulfadiazine every four hours; this therapy had been continued until admission. The temperature curve had remained unaffected. He had not noticed the presence of a rash until it was brought to his attention upon admission.

When admitted the patient appeared apathetic with a flushed face. His temperature was 101.8°F . (rectal) with a pulse rate of 92 per minute. There was a diffuse, red, maculo-papular erythematous rash over the arms, axillae and back. The macules were discrete, about 1 cm. in diameter and disappeared on pressure. No nuchal rigidity was present. Some few non-tender anterior cervical glands were felt. One large axillary node was palpable on the right side. With the exception of a palpable spleen, felt two fingers below the costal margin, the remainder of the physical examination was negative.

The hospital course was uneventful. With only symptomatic treatment, the fever which had ranged from 100°F . to 104.4°F ., fell by lysis and the temperature reached normal on the thirteenth hospital day. The pulse remained slow in relation to the fever. Soon after admission the rash began to subside and disappeared completely on the eighth hospital day, having

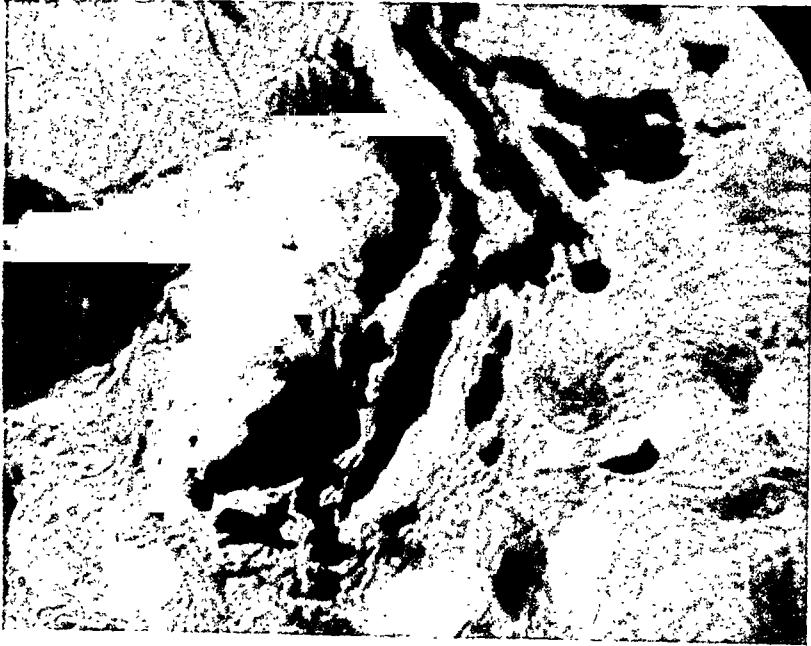


FIG. 2. B, section of skin macule; Giemsa stain $\times 2255$.

lasted until the sixteenth day of the illness. The spleen was not palpable after the sixth hospital day.

The laboratory findings showed several urine examinations to be negative. The hemoglobin and erythrocyte count were normal. On admission the leukocyte count was 11,050 with a normal differential count. It gradually fell to 8,700; the differential count showing an increase of lymphocytes from 22 to 45 per cent. The sedimentation rate was 78 mm. (Westergren). The Kline test was negative. Blood sugar and urea were within normal limits. Agglutinations for typhoid, paratyphoid, salmonella and brucella groups were negative, as were several blood cultures taken throughout the course of the illness. The heterophile antibody titer on admission and again on discharge was 1 to 16. Several stool cultures were negative. The Weil-Felix reactions for *Proteus* OX 2 and 19 were negative upon admission as well as ten days after discharge. Two months after the patient was discharged the Weil-Felix reaction showed a titer of 1 to 40 for *Proteus* OX 19. An electrocardiogram was within normal limits.

A skin biopsy was taken of a macule on the left chest on the sixth hospital day. Microscopic examination (Fig. 2A.) showed normal epidermis. The blood vessels of the upper part of the corium showed some swelling of the endothelial cells with some granular degeneration of the cytoplasm. There were occasional large histocytic cells near these blood vessels. A special stain (Giemsa) (Fig. 2B.) showed many of these swollen cells to be filled with minute bluish-black coccoid bodies in clumps within the cytoplasm. In some instances they occupied the entire cell. These were probably the inclusion bodies described as Rickettsiae.

SUMMARY

1. In the United States at present there seem to be three distinct types of rickettsial disease. Brill's disease (the American form of typhus fever) is found in the northeastern part of the country, murine (flea-borne) typhus occurs mainly in the southeastern part of the United States while Rocky

Mountain spotted fever (mite-borne) occurs throughout all parts of the country.

2. The pathological changes caused by Rickettsiae are essentially similar. These characteristic vascular changes consist of vasculitis and perivasculitis. If carefully looked for, the Rickettsiae may be found in the endothelial cells lining the blood vessels. The vessels usually affected are the smaller ones of the brain, lungs, skin and heart.

3. Successful treatment of the typhus group of fevers for the present depends upon starting therapy within the first week following the onset of the disease. Because of the difficulties in carrying out specific complement fixation and agglutination tests for Rickettsiae, a simple method of early diagnosis by skin biopsy is described.

4. Two patients with Brill's disease with characteristic clinical and pathological changes in the skin are presented. In one of the subjects, the rickettsial organisms were identified.

We are indebted to Dr. Irving Holtzman for aid in interpretation of the pathological slides.

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Virus Pneumonia

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PRIMARY atypical pneumonia, etiology still unknown, has become sufficiently prevalent since 1937 that a

three or four instances in which a clinical picture compatible with the modern concept of atypical pneumonia was encountered.

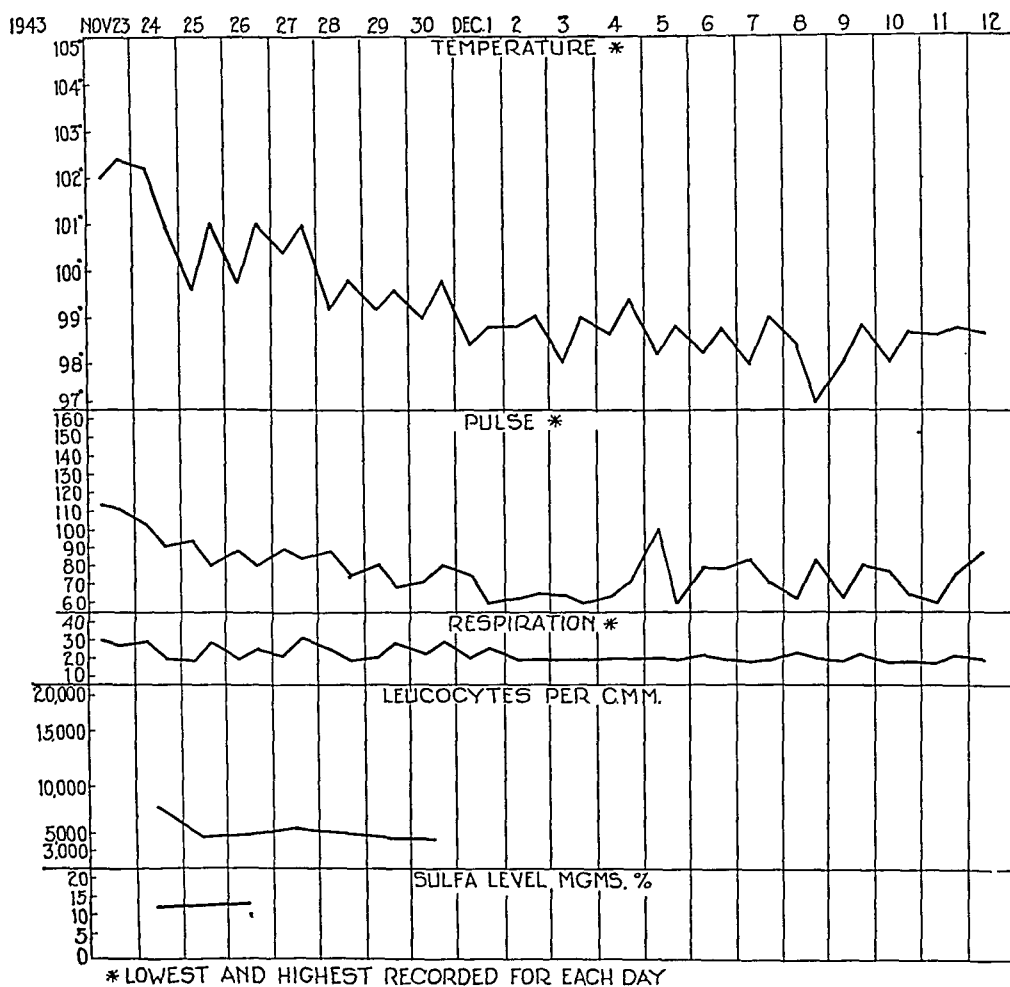


FIG. 1.

large number of publications have been devoted to its description.

Little more than a decade ago such cases were either exceedingly rare or went unrecognized. At that time the writer, during the course of two severe winters on a large pneumonia service, cannot recall more than

Does this mean that the incidence of this kind of pneumonia is increasing? It undoubtedly does because so many reports¹⁻⁶ have described a steadily increasing number of cases. In some army camps over 50 per cent, perhaps up to 75 or 80 per cent, of all pulmonary lesions have been primary

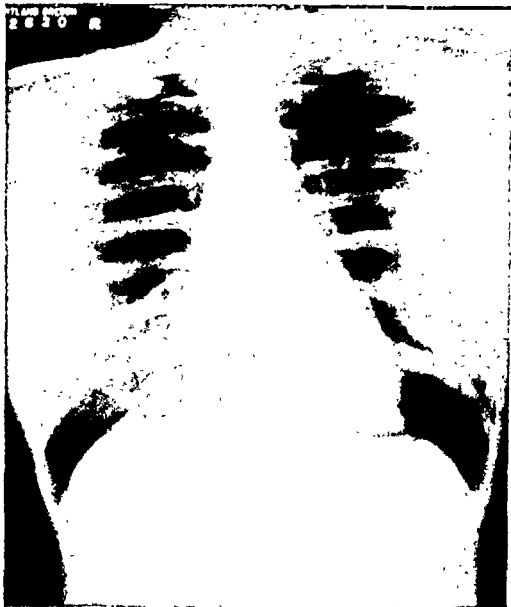
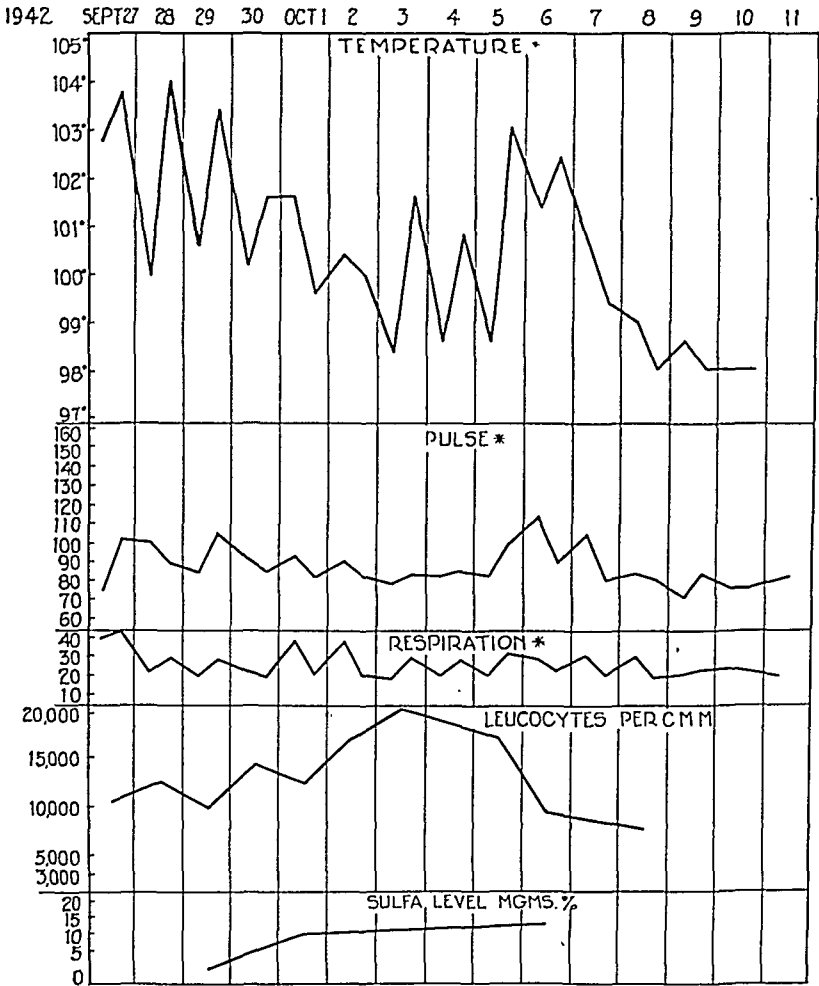


FIG. 2. Note the lacy infiltration, right base.



* LOWEST AND HIGHEST RECORDED FOR EACH DAY

FIG. 3.



FIG. 4.

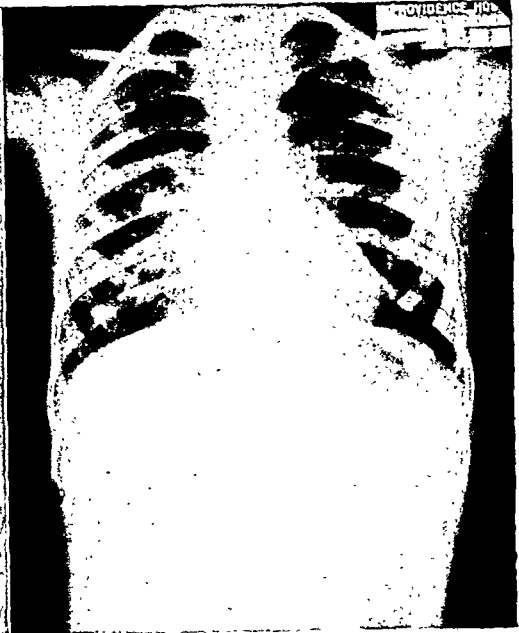


FIG. 5.

FIGS. 4 and 5. Involvement is extensive throughout the upper lobe (Fig. 4) but not very dense. Patchy pneumonitis (Fig. 5) in almost the entire right lung.

atypical pneumonia.⁷ Statistics in the civilian populace have not been so readily available but as high as 50 per cent of some communities have been involved because of a common viral agent.⁸

All are agreed that primary atypical pneumonia is not a new disease. Interstitial pneumonitis, a pathological picture indistinguishable from that produced by so-called "virus pneumonia," was fully recounted in the days of the Civil War.⁹ Likewise, both the clinical course and lung findings in the influenza pandemic of 1918 were very similar to those reported in present day autopsies of patients who died of primary atypical pneumonia.¹⁰

Ample opportunity for detailed study of a fair number of cases has been afforded every internist. Continued interest in the subject may result not only in fuller understanding of the disease as a whole but may well lead to definite recognition of the causative agent.

The present paper is based on an analysis of sixty-one cases which were studied be-

tween 1942 and 1944. These patients had all of the criteria essential to the diagnosis of primary atypical pneumonia: a respiratory disease of insidious onset, non-bacterial in nature, sometimes more striking roentgenologic findings than anticipated (more to be said on this later), leukopenia, normal white blood count or moderate leukocytosis, pulse and respirations low in relation to the temperature and failure of response to sulfonamides.

The etiologic aspects of virus pneumonia have been fully discussed by Reimann et al.¹² and many others.^{13,14} While current opinion favors the notion that the majority of cases of atypical pneumonia are due to some type of virus, it appears that other agents may be responsible for atypical pulmonary infection. The pathology has been adequately described elsewhere.^{14,15}

The clinical course in this disease is most variable and statements made concerning the severity of "virus" pneumonia are often grossly erroneous. That it is a mild or benign affliction may be true in most

instances, but it should also be pointed out that examples of critical illness are not unheard of, as one of my case reports will show. Some authorities have flatly stated that atypical pneumonia is not a contagious disease¹¹ but this is most fallacious. Others

is not included because he was neither hospitalized nor x-rayed.

CASE REPORTS

The following brief case reports, roentgenograms and graphs are presented to

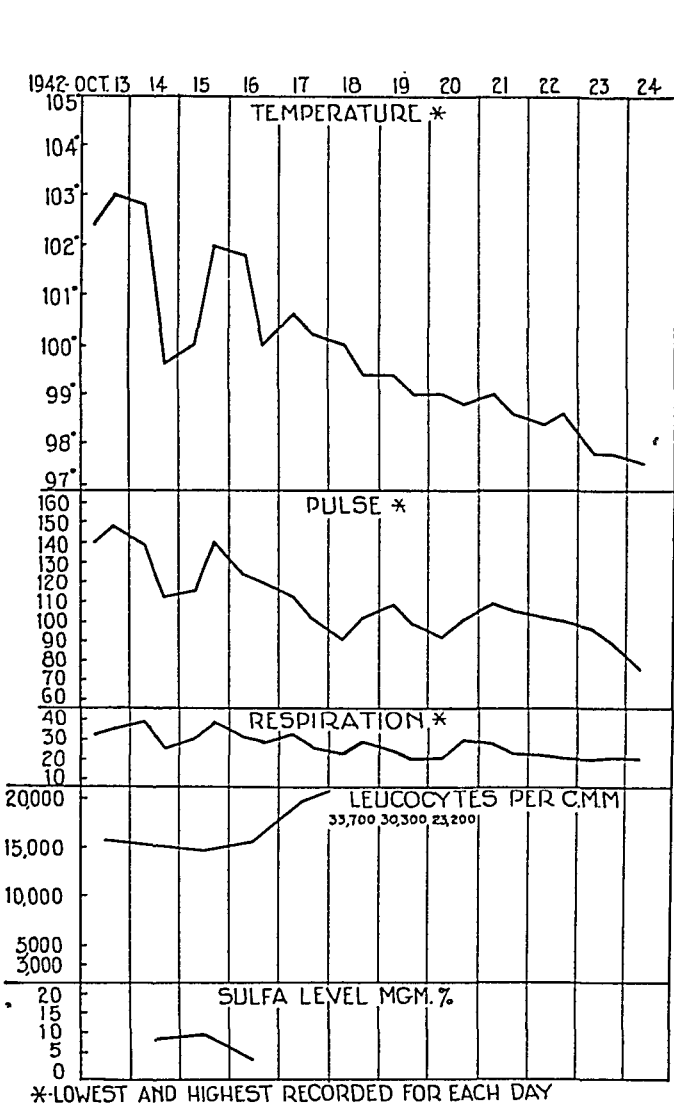


FIG. 6.

have stressed the low transmissibility to contact, but most authorities agree that it is highly communicable. The author had three cases in a family of five (the remaining two had a cold and cough) and another family of three in which all had "virus pneumonia" at the same time. Two of the last cases will be reported, but the father

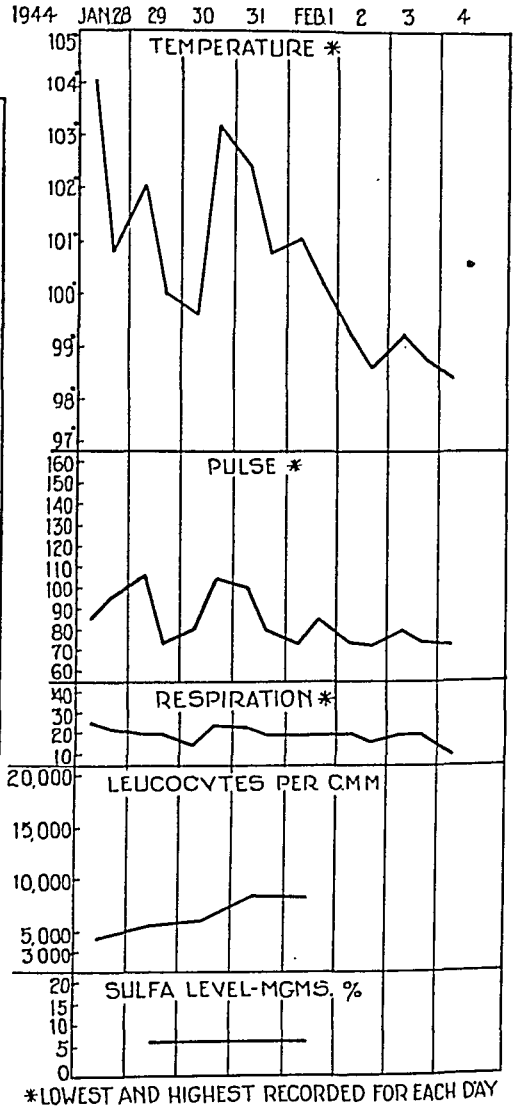


FIG. 7.

demonstrate some of the clinical aspects of this syndrome:

CASE 1. Mrs. W. A. S., a thirty-nine year old nurse, had been ill for about a week previous to her admission to the hospital on November 23, 1943. She had been having a slight fever, a dry non-productive cough, malaise, headache, feeling of extreme fatigue and depression. The day

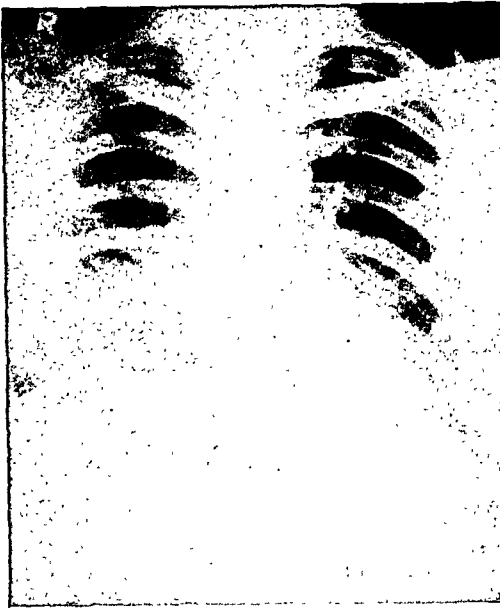


FIG. 8. The involvement here is chiefly right lower but there is also a patchy infiltration in the left lower lung field.

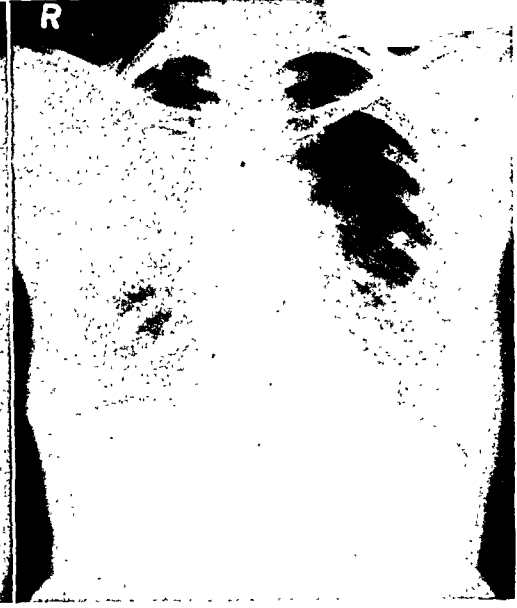


FIG. 9. This is one of the very occasional cases in which the x-ray findings were far more extensive than suspected.

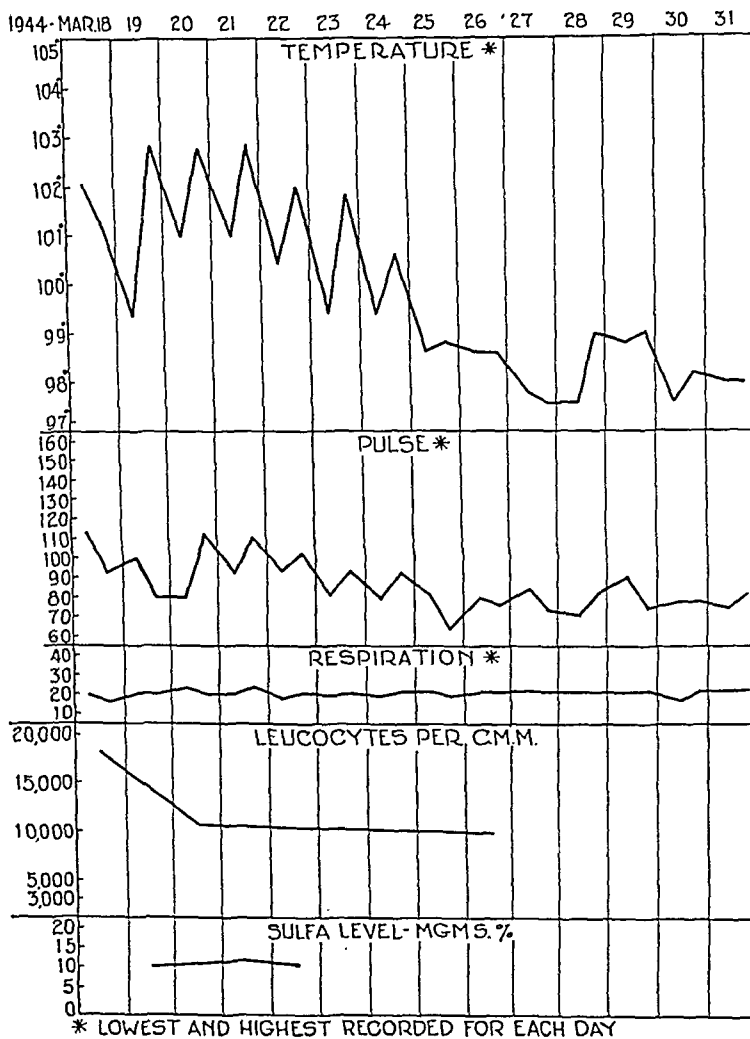


FIG. 10.

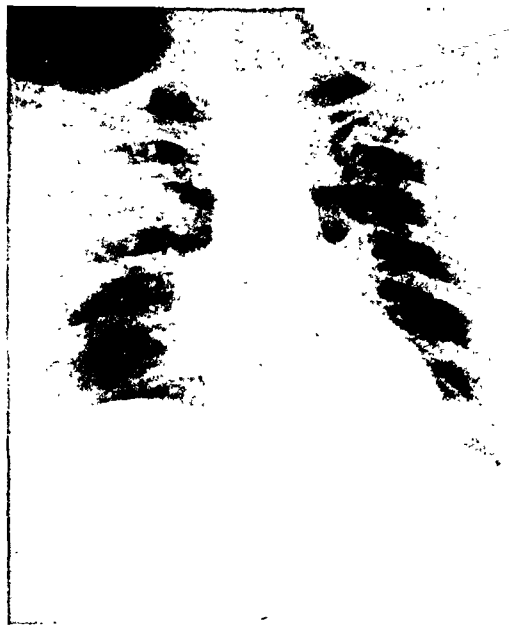


FIG. 11.

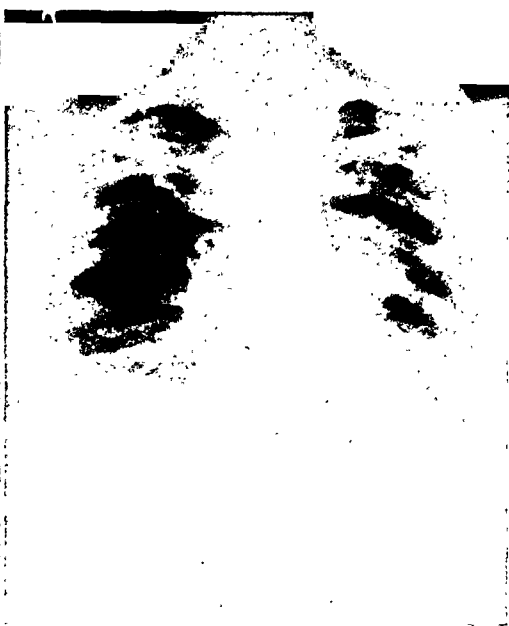


FIG. 12.

FIGS. 11 and 12. The lesion in the right upper in this instance (Fig. 11) had to be differentiated from tuberculosis. Recheck chest plate (Fig. 12) of patient shown in Figure 11 only six days later exhibits complete clearing of the right apex and the appearance of a small patch in the left lower lobe.

she was first examined, November 23, 1943, she did not appear acutely ill and her temperature was only 101.2°F. Physical findings were limited to slight impairment of resonance at the right base, and a few crackling râles upon deep inspiration; there was no suggestion of bronchial or tubular breathing.

From Figure 1 it is obvious that the fever was highest when the sulfadiazine level was 12 to 13, that the pulse is slow in relation to the temperature, and that the white blood count ranged from 4,000 to 7,900. It is worth noting that the roentgenologist in reporting the x-ray of this patient's chest (Fig. 2) stated without reservation, "virus pneumonia, right base." No organisms could be typed or grown from the sputum. Weakness and easy fatigability persisted in this patient for six weeks after recovery.

CASES II and III. Mrs. G. M. H. was twenty-seven years of age and her daughter, H. H., was aged three. The mother in this family of three became ill September 24, 1943, with chills, fever, headache, chest pain and later a hacking cough productive of a whitish, frothy sputum. She entered the hospital September 27, 1943, and at that time had dullness and râles in the

left upper chest. She was quite acutely ill and Figure 3 shows that the course of her temperature, etc., were not influenced by an adequate sulfa level and that coincident with the second elevation in temperature there was considerable leukocytosis. In the chest film (Fig. 4) pneumonitis of the left upper lobe is apparent. While this patient was in the hospital, her three-year-old daughter and husband became ill with cough, chills and fever. The former entered the hospital with a patchy pneumonitis involving most of the right lung. (Fig. 5.) The author is not so familiar with this type of pneumonia in children, but Figure 6 indicates that considerable leukocytosis may be present. The lack of response to sulfa is again exhibited. The husband and father of these patients had virus pneumonia at the same time but was treated at home. These cases illustrate that at least in some instances the disease is highly contagious.

CASE IV. R. B. G., a forty year old physician, is illustrative of one of the milder cases. He had the usual three-to-four-day prodromas of headache, malaise, chilliness and fever. He was placed on sulfa thirty-six hours before admission to the hospital, but Figure 7 shows that the

course of the disease was unaffected by its use. The cough remained non-productive. Figure 8 shows that the involvement was chiefly right but there is also some patchy infiltration in the left lower.

CASE V. Mrs. A. V. P. might be called a

some moist râles in the right upper lobe. Note the extensive involvement in the x-ray. (Fig. 9.)

This is the only example among the writer's cases in which the x-ray findings are greatly out of proportion to the physical

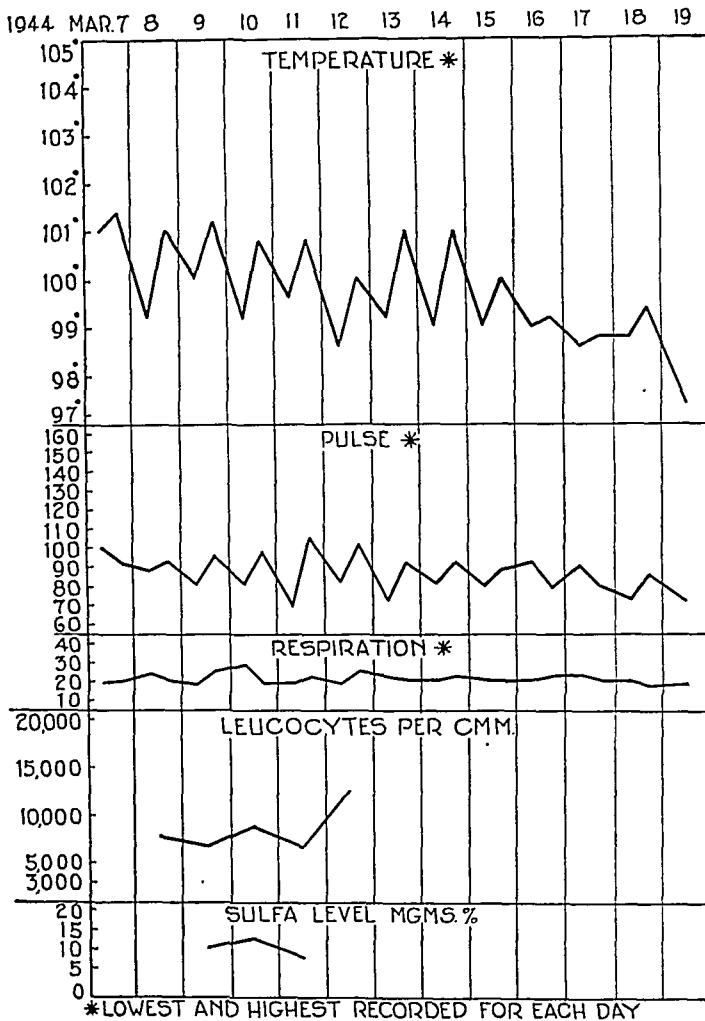


FIG. 13.

classical example of atypical pneumonia. For ten days previous to consulting a physician she had a daily temperature elevation from 100°F. to 102°F., headache and marked general malaise. Her husband was ill at the same time with similar complaints. She had a slight dry cough and did not appear acutely ill. Chest examination at first was entirely negative and it remained so until a frothy, grayish sputum began to be expectorated, at which time there were

findings. Massive consolidation is not a part of the pathological picture in atypical pneumonia, so naturally widespread dullness, loud tubular breathing indicative of large, solid areas in the lung parenchyma are not found. On the other hand, when carefully sought, the author has been able to demonstrate patchy areas of diminished resonance and crackling or moist râles and the latter

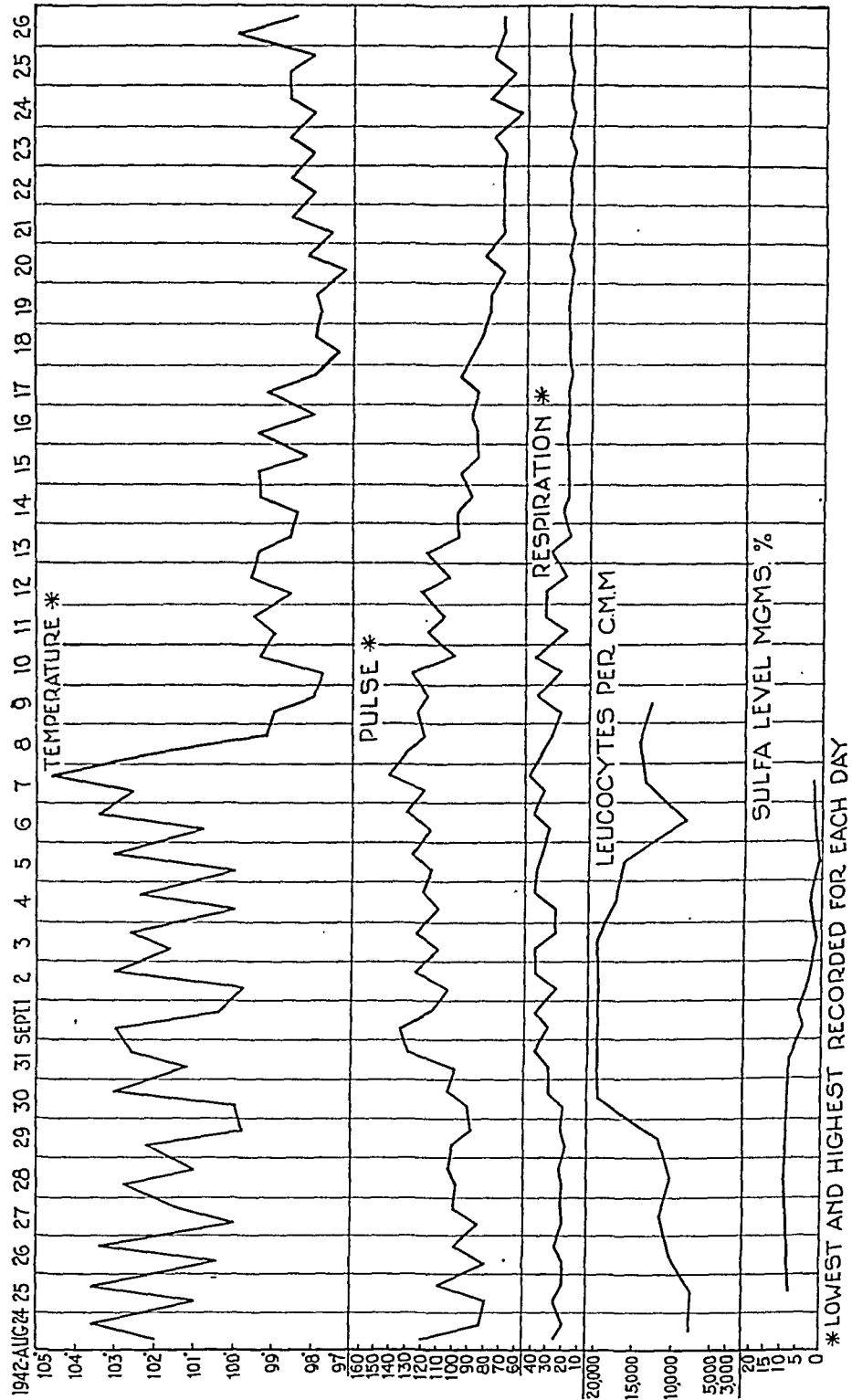


Fig. 16.



FIG. 17. Note the extensive pneumonic infiltration fanning out from the left hilum and extending into both upper and lower lobes, also the cardiac silhouette of mitral stenosis.

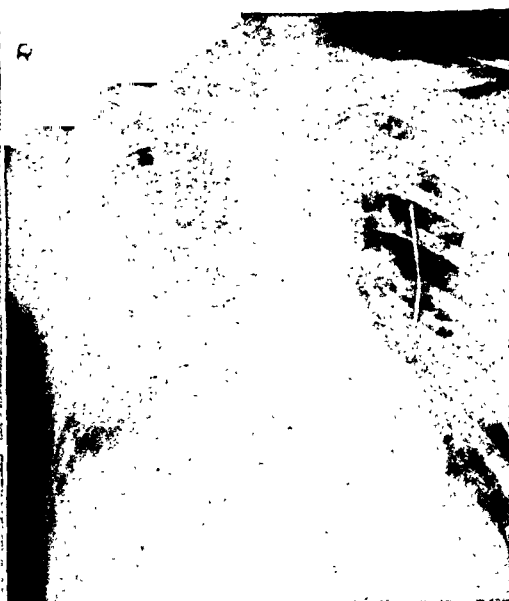


FIG. 18. Case VIII several days after film shown in Figure 17. This plate demonstrates slight resolution in the left lung and massive spread to the entire right lung.

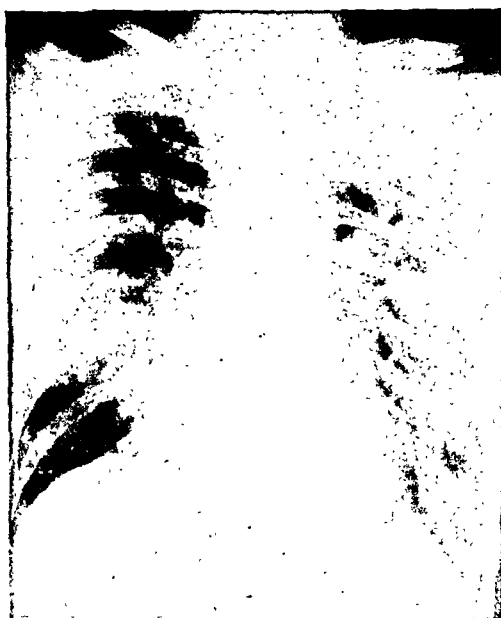


FIG. 19. This is the third film on Case VIII at which time his chest was clearing rapidly but the patient was nearly moribund from sulfa drugs.

2. Its course may be anything but "benign."

3. The disproportion between physical findings and roentgen findings has been overemphasized.

4. The ineffectiveness of sulfa therapy was repeatedly demonstrated and in one instance a near fatality followed persistence in its use.

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Recent Advances in the Diagnosis of Human Viral Diseases*

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NOT so many years ago, viruses and viral diseases still presented problems difficult if not impossible to solve by the usual laboratory technics. However, the accumulated evidence of the past two decades indicates that viral diseases follow certain well established patterns in which, to be sure, deviations from normal may occur as frequently or as rarely as in diseases caused by bacteria, fungi and other parasites. Although it does not seem likely that the diagnostic methods for viral diseases will become as simple as those for bacterial infections, numerous tools which facilitate diagnosis do exist. The following summary of such procedures has been written with the hope that it will stimulate some of the physicians hitherto overwhelmed by the perplexities of virology to face and explore the difficulties presented by a case of suspected viral etiology.

It is not the purpose of this review to describe and evaluate all the viral diagnostic procedures. The advance in virology has been so rapid, and the accumulation of literature in the field of diagnosis so great, that it is impossible to outline even briefly all of the recent developments. Therefore, the scope of this paper will be limited to the description of selected procedures which have proved of value in the diagnosis of viral diseases, and for convenience of pres-

entation will be discussed under the following headings: (1) Isolation of the virus, (2) dermal sensitivity tests, (3) serologic tests and (4) diagnosis based on ecology of the disease.

ISOLATION OF THE VIRUS

By far the most important diagnostic technic, both in viral and in bacterial diseases, is the isolation from the patient of the causative agent. Existing diagnostic procedures are time-consuming and consequently in some cases furnish only a retrospective diagnosis, and they require fair-sized diagnostic laboratories with adequate facilities and special equipment. In spite of these disadvantages, no effort should be spared since success in establishing a diagnosis often depends upon isolation of the virus.

Due consideration should be given to the possibility of the existence of virus carriers.¹ Only recently Meyer and Eddie² reported a case of a convalescent carrier who had harbored the psittacosis virus for eight years. Thus it is possible that one may isolate from a sick individual a virus which may have been dormant and only concomitant to another agent causing the diseased state. This occurred when Flexner and Amoss³ isolated a strain of herpes virus from a luetic

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patient who presented no signs of disease other than those of syphilitic infection. However, such instances are probably seldom encountered and fortunately certain serologic procedures to be mentioned later can often resolve such complications.

The type of specimen to be collected from the patient presents another problem for the physicians or laboratory workers who attempt to diagnose the disease by isolation of the virus. In making the selection, the tissue tropism of the suspected causative agent should guide the investigator. In most cases presenting involvement of the central nervous system, blood and spinal fluid may be used. In poliomyelitis, however, fecal material has been considered the best potential source of the virus. In dermal diseases of probable viral etiology, material obtained from skin lesions also may be tested for the presence of the causative agent. Sputum in general has been found a good source of virus in diseases involving the respiratory system, such as psittacosis² and other pneumotropic diseases of psittacosis-like etiology^{4,5} and the atypical pneumonia group.⁶ In cases in which the clinical syndrome indicates the presence of influenza virus, throat washings have been generally employed as test material.

However, in the past the presence of concomitant bacteria in throat washings was a serious drawback in the attempt to isolate the virus by the most effective and simplest method, that is by inoculation of the material into the amniotic cavity of developing chick embryos.^{7,8} Because of bacterial contaminants, death of the embryo often occurred before elapse of the period necessary for multiplication of the virus. Introduction of sulfa drugs and of antibiotics helped to overcome this obstacle. For instance, by simultaneous inoculation of penicillin into the amniotic cavity, Hirst⁹ isolated the influenza virus from untreated throat washings and prevented bacterial

invasion of the embryo. Burnet and Stone¹⁰ found the use of sulfadiazine solution equally effective, and McKee and Hale¹¹ employed streptomycin for the same purpose. The bacteriostatic action of antibiotics has been useful in the isolation of agents other than that of influenza, for example, of mumps virus from infected saliva.¹² Hodges¹³ was able by simultaneous administration of combined solutions of streptomycin and penicillin to combat bacterial growth in chick embryos inoculated with fecal suspensions.

However, in most cases suspected of viral etiology the blood of the patient probably represents one of the best potential sources of the virus. The literature dealing with isolation of viruses from the blood or sera of patients is too extensive to be cited here but the following factors should be considered when isolation of a virus from the blood is being attempted:

1. Blood should be drawn as soon as possible after the onset of illness. The rise in circulating homologous antibodies during the later stages of the disease may cause the disappearance of the virus from the blood stream or, by the simultaneous introduction of immune bodies, may hinder isolation of the virus in the experimental animals.

2. Failure to isolate a particular virus from the blood of patient in a given disease does not necessarily imply that a virus cannot be isolated from the blood in other cases of similar etiology. Whereas in poliomyelitis the virus has been isolated on several occasions from nasopharyngeal swabs, oropharyngeal washings¹⁴ and stools of patients,¹⁵ as well as of contacts,¹⁶ in only one of 111 samples tested had the virus been found in the blood.¹⁷ Nevertheless, by means of blind passages in mice our laboratory has succeeded in isolating a virus from the serum of a mild case of poliomyelitis. This virus was neutralized by convalescent serum of the patient, and subsequent tests

showed that it bore the characteristics of poliomyelitis virus.¹⁸

After the material is collected with due precautions for sterility, the question arises how to handle it. Should it be delivered to the nearest diagnostic laboratory, or should it be inoculated immediately into a presumably susceptible host at the "bedside" of the patient or at the physician's office? In rural sections, this question is of importance. Should the physician object to bringing animals to his office or to the home of the patient, he can avail himself of two other procedures. One is the technic of inoculation into a developing chick embryo, which is simple enough to permit its application without laboratory facilities,¹⁹ and the other is the use of previously prepared tissue culture flasks.²⁰ However, as soon as the primary inoculation is made by the physician, the inoculated host or medium should be delivered, together with samples of the original specimen, to the nearest viral diagnostic laboratory for the proper testing. Should delay occur, the original material as well as the tissue harvested from the experimental animal host should be placed in a dry-ice unit, if available, or in the freezing compartment of an ordinary refrigerator. During transit the material should be kept properly chilled.

There are three accepted methods for primary isolation of viruses: animal inoculation, chick embryo inoculation and the addition of the infected material to tissue cultures. The practicability of the latter technic in the field has not been sufficiently tested as yet and except for the primary isolation of epidemic kerato-conjunctivitis virus in tissue culture,²¹ no new developments have been reported. This leaves animals and chick embryos as the most widely employed hosts for primary isolation of viral pathogens.

The results of inoculation in laboratory animals may help not only in establishing

the causative agent in an experimental host but, depending on the host range of the virus and the susceptibility of the animal to different routes of inoculation, may also aid in establishing the diagnosis. Space does not permit discussion of the host range of different viral agents but brief mention will be made of a method by which the response of the mouse may serve to identify the virus among the so-called neurotropic viruses.²² Let us assume that a group of twenty-eight-day old mice, and another group of fourteen-day old mice, are inoculated with the same material by a parenteral route. If mice in both age groups succumb to infection, one of the equine encephalomyelitis viruses was probably present in the inoculum. However, if the twenty-eight-day old mice survive and the fourteen-day old mice succumb, either St. Louis or Japanese B encephalitis virus may be present.²² The above example, of course, is hypothetical and greatly simplified. However, by means of correlation of data relating to age of animals, mortality ratio and average survival time, the pathogenic properties of the unknown agent may be so similar to those of a recognized virus that a diagnosis may be postulated with considerable accuracy. For instance, on the basis of these factors it was shown that the St. Louis encephalitis virus was the causative agent in a fatal case of encephalitis recently reported in California.²³

Formerly, primary isolation of virus in experimental animals often failed because of low concentration of the virus in the original inoculum. Today this is overcome either by concentration of the virus in the original inoculum by Sharples centrifugation,²⁴ as can be done with poliomyelitis virus in stools and sewage, or by the so-called blind passage technic. The rationale of the latter method is based on the assumption that multiplication of the infectious agent in the initial host is of such a low

order that no apparent clinical signs of the disease are elicited. However, if the animal is sacrificed and the presumably infected tissue passed into another host of the same species, multiplication of the virus in the second-passage host may be rapid enough to elude perceptible signs of illness. During the recent outbreak of Q fever in the United States, the causative agent was isolated from human serum by blind passages in dilute brown agouti mice;²⁵ the above mentioned isolation of poliomyelitis virus¹⁸ was also attained by the blind passage technic. Moreover, if the serum already contains antibodies, it is possible that by blind passages in laboratory animals the viral agent may be more easily "divorced" from the antibodies and thus an experimental infection in animals be established. It is highly recommended that an adequate portion of serum sample be set aside for the comparative serologic tests, which will be described later. About 20 to 25 ml. of blood obtained during the acute phase of illness should suffice to cover all requirements.

The chick embryo technic has been employed for the isolation of influenza virus,^{7,8,26} for herpes virus from penicillin-treated sputum of gingivostomatitis cases and, as already mentioned, for mumps virus.¹² Those interested in the advantages and disadvantages of the use of chick embryos and the practical application of different technics are referred to the comprehensive and excellent monograph recently published by Beveridge and Burnet.²⁸

After the experimental infection presumably originating from the human source has been established in a laboratory host, the next step is identification of the agent. Methods employed are described under serologic tests.

DERMAL SENSITIVITY TEST

In diseases of bacterial origin, intracutaneous injections of antigen have been

chiefly employed to determine the immunologic status of the individual. In the field of viral diseases, the few dermal sensitivity tests developed serve primarily not as diagnostic procedures *per se* but as evaluations of susceptibility to a given viral disease. A notable exception is the modified Frei test in which antigen prepared from yolk sacs infected with the virus of lymphogranuloma venereum elicits a dermal hypersensitivity reaction in infected individuals.²⁹

If herpetic infection persists during the lifetime of an individual^{30,31} the *Herpes simplex* dermal sensitivity test developed by Nagler^{32,33} may be used as a diagnostic procedure. On the basis of results obtained with the test in fifteen adults subject to labial herpes and fifteen non-herpetic individuals,³³ Nagler came to the conclusion that the test is diagnostically specific.

Beveridge and Burnet³⁴ inoculated adults and children intradermally with influenza A or B virus-infected allantoic fluids to determine their immunologic status. Most of the adults gave positive skin reactions while of thirty-one children only eighteen reacted positively and of these all but one were reported to have had infection with one or the other type of influenza virus.

Enders et al.³⁵ described a dermal sensitivity test for mumps in which heated parotid glands of infected monkeys constituted the reagent. The experimental results indicated its specific value as a retrospective diagnostic,³⁵ or as an indicator of an immunologic status following vaccination.³⁶ Finally, reagents prepared from yolk sacs infected with meningopneumonitis or with psittacosis viruses have been found to produce erythematous skin reactions in rabbits convalescent from meningopneumonitis infections.³⁷

While data at present are still rather meager, the dermal sensitivity tests merit further research because of their potential importance as diagnostic procedures. How-

ever, the increasing number of allergic reactions to vaccines of chick embryo origin³⁸ may diminish their value unless practical means can be found to free the test reagents of chick proteins.

SEROLOGIC TESTS

It has already been pointed out that the procedures for isolation of virus are time-consuming and thus may cause a delayed diagnosis. Serologic tests, if correctly performed, may be of immediate diagnostic value. Parallel tests should be run on two blood samples drawn from the same individual, one drawn during the onset of the illness and the other drawn several days later. Demonstration of antibodies in a single sample of serum, when accompanied by a typical clinical course, may indicate the correct diagnosis, but only a rise in antibody titer constitutes proof. A correct and rapid diagnosis is of particular importance in viral diseases which may occur as latent infections, such as psittacosis in children.² Apparently, this viral disease is one of the few that can be cured by sulfadiazine and penicillin therapy,³⁹ or by penicillin alone.^{2, 40, 41, 42} The criteria of "cure," however, should be carefully determined since in penicillin-treated mice the infection becomes latent and the animals become psittacosis carriers.^{43, 44} As stressed by Meyer and Eddie,² a properly performed complement-fixation test is of great diagnostic value. In one of their penicillin-treated patients the immunity response was prompt, as shown by rise of complement-fixing antibodies. At the end of ten months the antibody titer had diminished considerably and the authors concluded that "the tissues had been largely freed of the viral agents."

In recent years substantial progress has been made in complement-fixation tests for neurotropic viruses. Antigens without anti-complementary action, prepared from infected mouse brains by Casals and Palacios,⁴⁵

were used for diagnostic purposes in the study of an encephalitis epidemic which was shown to have been due to the Western equine encephalomyelitis virus.⁴⁶

Until recently the use of antigen prepared from infected mouse brains was handicapped by non-specific fixation in the presence of Wassermann-positive sera. The recently developed technic⁴⁷ of preparing lipoid-free antigen by benzene extraction after lyophilization eliminates such false positive reactions. This method has been used successfully in preparing antigens for Eastern and Western equine encephalomyelitis, St. Louis and Japanese B encephalitis,⁴⁷ rabies⁴⁸ and Colorado tick fever.⁴⁹

Mumps is another viral disease which recently has received greater attention. A typical case of parotitis can be diagnosed easily because of the unmistakable clinical picture but for atypical cases in which involvement of the central nervous system is the only sign of disease diagnostic methods were not available until Enders and his associates³⁵ developed a specific complement fixation test. Using parotid gland tissue of an infected monkey as antigen, Kane and Enders⁵⁰ were able to diagnose cases of meningo-encephalitis in which involvement of the salivary glands was either slight or absent. Since the complement-fixing antibodies appear with regularity and within a short period after onset of the disease, a new diagnostic tool was made available. However, it should be stressed once again that two specimens of blood should be drawn at intervals of one to two weeks³⁵ for the complement-fixation test in order to establish a rise in antibody titer which may be considered as diagnostic proof.

The complement-fixation test also provided a means for demonstrating the adaptation of mumps virus to the developing chick embryo,⁵¹ and subsequent evaluation of the egg-adapted virus for immunization experiments.⁵²

The hemagglutination-inhibition test is even less time-consuming than the complement-fixation test. So far it has been used extensively in immunologic studies on influenza virus. In studies comparing the complement-fixation with the hemagglutination-inhibition test, Dalldorf and Rice⁵⁴ obtained similar results with both technics in a state-wide survey of sera collected in New York state. Hemagglutination has been reported with the viruses of mumps⁵⁵ and of vaccinia⁵⁶ but application of the hemagglutination-inhibition test in these two diseases has not yet been described.

In some neurotropic viral diseases the neutralizing antibodies may appear earlier in the course of the disease than the complement-fixing antibodies. Sabin,⁵⁷ in his study of Japanese B encephalitis among military personnel, described four cases in which the presence of neutralizing and the absence of complement-fixing antibodies was demonstrated between the third to seventh days after the onset of illness. However, because of the time-consuming nature of the neutralization test, results often become available during convalescence, or even posthumously in cases of fulminant encephalitides. Because, in general, the neutralizing antibodies appear early in the course of the disease neutralization tests should be performed on two samples of sera to record any rise in antibody titer.⁵⁷ The neutralization test, especially if performed by the parenteral route in mice,⁵⁸ represents a more sensitive technic than the complement-fixation test when the susceptibility or resistance to a given viral disease is to be determined. In some diseases, e.g., yellow fever, post-vaccinal immunity can be determined only by a neutralization test.

In describing serologic tests in viral diseases, two tests should be mentioned which are used for diagnostic purposes in a disease of unknown but probable viral

etiology, that is, in primary atypical pneumonia. These are the cold hemagglutination test⁵⁹ and the agglutination test against a non-hemolytic MG streptococcus.⁶⁰ Available data on both tests, recently summarized by Horsfall,⁶¹ have shown MG streptococcus agglutination titers of 1:20 or higher in 48.9 per cent, and cold hemagglutinin titers of 1:40 or higher in the sera of 54.4 per cent of patients with primary atypical pneumonia. If the tests are performed on two or more samples of sera from the same patient a rising titer increases the diagnostic significance of the results.⁶¹

In concluding the description of serologic tests as diagnostic procedures, mention may be made of the precipitation test developed by Olitzki and Bernkopf in infectious hepatitis.⁶² Using a cholesterolized alcohol extract of ether-treated spleen or liver tissue, these investigators were able to demonstrate differences in precipitin titers in sera obtained from patients with infectious hepatitis and those ill from some other disease. Much more evidence is needed before this technic can be accepted as a reliable test.

DIAGNOSIS BASED ON THE ECOLOGY OF THE DISEASE

This phase, unfortunately, has received very little attention in the past. Actually, a careful ecological study may furnish clues to diagnosis. This applies in particular to viral infections transmitted from animals to man, or from man to man, by vectors. It is of lesser importance in diseases transmitted by fomites, water or milk. But even in the latter category, as for instance in infectious hepatitis, careful questioning of the patient about association with jaundiced persons, administration of blood or plasma,⁶³ may reveal data of diagnostic importance.

An example of how ecologic study may lead to isolation of a new pathogen has been furnished recently by a group of

investigators who described rickettsialpox.^{64,65,66} Finding a housing development infested with mites and mice where more than eighty cases had occurred, a field laboratory was set up for the study of their rôle in the disease. Apparently identical strains of rickettsia were recovered from a patient ill with rickettsialpox, from blood-sucking mites collected in the house of the patient, and from a mouse bitten by mites.⁶⁶

During the recent occurrence of Q fever in the United States, a diagnostic clue was furnished by the outbreak occurring among live-stock handlers and slaughter-house workers, incriminating cattle as the source of the infectious agent.⁶⁷ Lymphocytic choriomeningitis is another viral disease in which ecologic study may help in establishing a diagnosis. Armstrong and Sweet⁶⁸ isolated the virus from gray mice caught in houses in which two human cases had occurred. Whereas mosquitoes,⁶⁹ ticks⁷⁰ and lice⁷¹ have been found infected with the virus, the above report, as well as the one by Farmer and Janeway,⁷² incriminates mice chiefly in the ecology of lymphocytic choriomeningitis. A case of involvement of the central nervous system occurring in a mouse-infested building should no doubt be considered a potential case of lymphocytic choriomeningitis but because of the frequent recovery of the virus from mice⁷³ consideration of some other causative agent should not be excluded.

There is probably no other viral disease in which study of ecologic conditions is of greater importance than in psittacosis and psittacosis-like diseases. In cases of non-bacterial pneumonitis giving a history of contact with psittacine birds, pigeons, canaries, finches, chickens or sea gulls, psittacosis should be suspected.² Psittacosis-like agents have also been isolated from laboratory mice, ferrets, cats and kittens.² Recently, Pollard⁷⁴ found serologic evidence

of a psittacosis-like infection among sea gulls, skimmers and willets, and isolated a psittacosis-like agent from the latter species. Dr. Korn, in his discussion of the presentation by Meyer and Eddie,² described an ecologic study of psittacosis on Long Island which incriminated ducks as the source of the epidemic, and duck handlers as psittacosis carriers. Of course not every case of non-bacterial pneumonitis is due to the psittacosis virus, yet a physician who is called to treat such a patient should bear the possibility in mind and report a careful "ecologic record" to the nearest viral diagnostic laboratory.

CONCLUSION

A brief review obviously cannot include all the pertinent data on viral diagnostic procedures and a word of caution should therefore be added. There is a tendency to oversimplify these diagnostic procedures, and very often apparently correct conclusions are drawn from false experimental data. In viral diseases the living experimental host is comparable to the differential bacteriologic media. But the resemblance stops at this point. The experimental host, being a living organism, may harbor an agent or agents which may give rise to a "spontaneous" infection at a time when the inoculated material is expected to elude clinical symptoms. Such an occurrence may not only puzzle an inexperienced observer but may also lead to an erroneous diagnosis. If at any time a clinician has any doubt of his ability to interpret the reactions of an experimental animal to an inoculum, it is highly advisable that he immediately forward the original specimen from the patient, together with the experimental host, to the nearest viral diagnostic laboratory.

Better understanding of the nature of viral diseases has been achieved mainly through the effective cooperation of the

clinicians, pathologists, epidemiologists and diagnostic research laboratories. With the continued teamwork of all concerned further developments may be expected.

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Operative Treatment of Venous Thrombosis in the Lower Limbs

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BECAUSE the thromboembolic problem is now being attacked with a reasonable hope of success from two seemingly opposed points of view, it is proposed here to evaluate the means of treatment in use today. Historically, efforts to prevent fatal pulmonary embolism go back into the last century. These efforts have been applied chiefly to postoperative thrombosis as its source with the idea of preserving a normal physiologic condition for the circulatory and muscular systems, a plan which is only partly covered by the term "early ambulation." Some ten or fifteen years ago, it seemed that all that could reasonably be expected had been accomplished. It is only since a newer understanding of the origin and course of venous thrombosis in the lower limbs has been gained that further progress has been made. Briefly, this understanding relates to the occurrence of a quiet, reactionless disease beginning below the knees, and to various grades of this process tending toward and often developing into obstructive inflammatory lesions at a higher level. Attention is thus drawn from an end result—phlegmasia alba dolens—to an early, propagating and therefore dangerous stage of thrombosis. It is also drawn to the inter-relationship of lower limb thrombosis and serious disabling disease in general, especially heart disease, and to the occurrence of thrombosis in seemingly normal, active individuals. Naturally, treatment attempts to

halt and heal the quiet process at the earliest possible moment and to abolish its dangers. To make clear the principles underlying such treatment there is offered here first a summary of the significant aspects of the disease.

Venous thrombosis starts in the calves, feet, thighs and pelvis (in that order). More than 90 per cent of such thrombosis originates below the inguinal ligaments. Its usual cause is anything disabling which enforces life in bed, namely, operation, disease, injury or childbirth. Its incidence, and especially its liability toward pulmonary embolism, increases with age being greatest during the time from fifty to seventy years of age. Unpredictably and without obvious cause it crops up at any period of active life. In a mixed hospital population not more than 25 per cent of thromboembolism is postoperative and 50 per cent is medical, chiefly as a complication of heart disease. From its origin thrombosis tends to progress upward from a single deep vein or group of veins, causing little or no obstruction to the venous return of blood until it fills the main femoral stem. In its early, quiet form or stage it is known as *phlebothrombosis*. From such a process a friable thrombus, or perhaps better a clot, is apt to break off causing pulmonary embolism. Although thrombosis tends toward a late, outspoken, obstructive stage, namely, *thrombophlebitis*, it may heal rapidly without reaching it, persist even for months without reaching it, or cause death by embolism. In fact, the disease

may have from the start a quiet, propagating, reactionless character, or a more outspoken, inflammatory quality. Most thrombosis is bilateral, yet it is almost always more advanced and obstructive in one leg than the other. Thrombosis necessarily leaves the veins it invades functionless by crippling their valves, but not permanently obstructed since canalization usually occurs. Thrombosis is found, if carefully sought, in about 50 per cent of all autopsies, the greater proportion being terminal, indicating merely the effect of enfeeblement, venous stasis and confinement to bed. Unless prevented, thrombosis occurs in about 1 to 2 per cent of all "surgical" cases; pulmonary embolism of some degree occurs in about 50 per cent of all "surgical" thromboses, and fatal embolism in about 20 per cent of such thromboses. Although some individuals are, for reasons unknown, more liable to thrombosis than others, many of those in whom thrombosis has become established become increasingly thrombophilic—a few almost uncontrollably so.

Pulmonary embolism shows itself in an embolic phase and as infarction. Embolism is suggested by an attack (otherwise unaccountable) of rapid or difficult breathing, of angina-like distress, of syncope (reflex circulatory failure) or of right-sided heart embarrassment. To such disorders, electrocardiographic evidence may offer support. Infarction is indicated by thoracic pain, cough and hemoptysis, and may follow symptoms of embolism or come from a clear sky. In the presence of congestive heart failure, hemoptysis is almost pathognomonic. But it should be recognized that pulmonary embolism may arise from thrombosis in the right heart as well as from the lower limbs. Infarction is best recognized in a thorough, out-of-bed, x-ray examination of the thorax.

The diagnosis of thrombosis may be inferred from the discovery of pulmonary embolism, even in the absence of local signs

in the lower limbs. It is strongly suggested by an elevation of pulse, temperature and respiration, best seen against a level background—an elevation which may perhaps be accounted for by "preclinical" pulmonary infarction. Local signs in the legs include increased muscular firmness of the calf or actual irritability of the great posterior muscles. Even slight enlargement is significant but edema, cyanosis, tenderness or actual pain are relatively late signs. All signs lag behind the progress of the disease in patients fully confined to bed.

Thrombophlebitis (*phlegmasia alba dolens*) not only obstructs the femoral and more or less of the iliac veins, together with a variable number of collaterals, but reflexly occasions constriction of the finer blood vessels causing edema of the whole limb and occasionally constrictions of the larger arteries (axon reflex or local effect). The diffuse peripheral vasoconstriction is often released by sympathetic paralysis (lumbar sympathetic block) and by emptying the vein of thrombus. The most favorable effects of treatment are secured before thrombophlebitis has existed for many days. Embolism is rare but cannot be ignored. Loss of its valves and subsequent loss of function in the femoral system (no valves are found in the external or common iliacs) cause most of the bad late results of thrombosis. These are edema of the limb and the development of fibrosis and ulceration in the lower leg. Secondary disablement of lymph drainage is a contributing factor. Pain complexes and secondary varicosity also occur. Veins once thrombosed and canalized are liable to recurrent thrombosis but not necessarily to embolism.

TREATMENT

Though thromboembolism has usually been regarded primarily as a surgical and obstetrical accident, it has actually, as already indicated, as great medical as surgi-

cal significance. Yet so much of the thromboembolism of cardiac and other serious disease is *terminal* that its exact rôle in the morbidity and mortality of a medical service is exceedingly difficult to determine. The operative and chemical treatment of venous thrombosis must take into account this aspect of the problem. In presenting the operative side, I shall indicate very briefly my understanding of the relative therapeutic value of anticoagulant therapy as well as the circumstances under which the two may properly be combined.

Prophylactic Operative Treatment. This has been carried out consistently for several years by Dr. Arthur W. Allen, Dr. Robert R. Linton and their associates^{1,2,3} at the Massachusetts General Hospital. The procedure is confined, for all practical purposes, to surgical patients of fifty years and over, subjected to operation in one or more stages for cancer and other serious abdominal, pelvic and thoracic diseases. Because of the frequency of thromboembolism as a complication of fractures of the upper femur and of amputations for arterial disease of the legs, these two categories are included. Some few cardiacs have also been subjected to similar prophylaxis.

Bilateral ligation of the femoral vein distal to and as close as possible to the profunda branch is the procedure used. In skillful, trained hands, the ligation may be combined with the underlying major surgical operation. If not so combined, it is separately performed under a local infiltration anesthetic. Dr. Allen and his associates report the results of 521 such operations to October 1, 1946. Among 458 patients, sixty-five years and over, there occurred one fatal embolism, a relatively small number of thromboses and very few unpleasant after-effects (less edema, etc.) than follows definitive treatment of established thrombosis. Such prophylactic treatment fails, of course, to cover the entire field, since con-

siderable thrombosis (18.5 per cent) occurs in the fifth decade, and it ignores the rare thrombosis of pelvic origin. But since it has seemed impracticable to include patients of all ages down to forty, relegation of those in the younger group* to prophylactic anticoagulant therapy, or to definitive treatment as thrombosis arises, is obviously reasonable.

There is no proof from available statistics that prophylactic treatment with either heparin or dicumarol offers superior protection for the dangerous group in question. There are reports from the Mayo Clinic (Barker et al.),⁴ from Murray⁵ and from Crafoord⁶ and others (Sweden) showing 100 per cent prophylactic postoperative protection by the anticoagulants, but none covers the concentrated, difficult field just mentioned. The same is probably true of gynecological surgery in which comparative figures should soon be available. Although they are not dealing with the problem of prophylaxis, Evans and Boller,⁷ in their recent study of fatal embolism at the Lahey Clinic, point out that though intensive postoperative observation, in preparation for anticoagulant therapy of such thromboembolic disease as may be discovered and treated, has lowered still further the already low figures of fatal pulmonary embolism in that clinic, a little group remains (forty-eight in 45,000 major surgical operations from 1940 to 1946) as a problem. In some instances (my comment), routine anticoagulant prophylaxis could hardly have been used and surgical prophylaxis would have been desirable, but to apply prophy-

* I understand that the low age for prophylactic ligation, in connection with a limited variety of operations, is now fifty years. According to Allen, Linton and Donaldson,¹ thrombosis was noted in their control series as follows:

Age	Percentage
40-50	18.5
50-60	25.3
60-70	22.9
70-80	13.1
	61.3

lactic bilateral femoral vein ligation to thousands of patients to save only the ten to twenty whose causal thrombosis could not otherwise have been controlled would seem to be carrying surgery pretty far.

Finally, prophylactic bilateral femoral vein ligation must be performed so skillfully as to result in no accidents whatever related to the operation *per se*. Like anticoagulant therapy, it actually attempts to save so very few that it must injure none. That such can be accomplished in any but specially organized clinics, I very much doubt.

DEFINITIVE TREATMENT

Femoral Vein Ligation. Let it be agreed that a diagnosis of venous thrombosis in one or both lower limbs, whether or not pulmonary embolism has occurred, calls for definitive treatment by vein interruption or anticoagulant therapy. The unavailability of dicumarol or heparin, and especially the unavailability of laboratory tests required for their use, serious disease of liver and kidneys, ulceration within the stomach or intestine, and any hemorrhagic disorder (though such does not seem to threaten thrombosis) may be considered contraindications for anticoagulant therapy and therefore indications for ligation. Once venous thrombosis is diagnosed, persistence of conditions threatening thromboembolism, such as two-stage operations, long confinement to bed by fractures and other injuries, and debility due to diseases requiring a continuous reclining position, are counted positive indications for surgical vein interruption.

The simplest surgical procedure is ligation or section of the femoral vein. The operation must be bilateral. The level at which interruption is to be performed is the debatable consideration. Just proximal to the profunda branch, but distal to the saphenous opening, ligation is most effective in preventing embolism, but this point is a

“bottle-neck” and if thrombosis has already involved many collaterals in the thigh a serious degree of stasis and edema will follow. There may even occur an *immediate* serious venous congestion, causing local damage to the limb and some degree of shock. Yet if the femoral vein is ligated distal to the profunda, leaving this great branch open, fatal embolism from this source will occasionally and unpredictably occur. Even a very early lower leg thrombosis is not necessarily controlled by a distal (superficial femoral) ligation. For all that, many proponents of operative treatment prefer the ligation distal to the profunda to that of the common femoral vein, even when they have been obliged to extract soft thrombus by suction from the common femoral and iliac veins.

As to the above problem, I offer the following comments: (1) In a good many instances, superficial femoral vein ligation can be reinforced for the few days before bed-life can be abandoned with anticoagulant therapy; (2) if the common femoral level is selected, a very carefully supervised postoperative course—active exercise in periods of depression alternating with exercise and drainage by elevation—will often establish an excellent collateral circulation and minimize edema; (3) though it is true that once thrombosis has occupied the femoral vein this vessel must become functionally useless whether anticoagulant therapy or surgical interruption is employed, sudden operative closure of the femoral “bottle-neck” has seemed to me a little more crippling than treatment by anticoagulants and (4) even though (3) is true, an advanced thrombosis—the individual being increasingly thrombophilic—is better controlled by vein interruption than by anticoagulant therapy. It is fair, then, to say that surgical judgment and familiarity with the behavior of thrombosis under various conditions will govern the level of

the standard vein interruption. Rules are easy to make and hard to keep. In the following paragraphs I will indicate situations requiring special consideration, namely, thrombosis arising in active individuals, thrombosis without pulmonary embolism and thrombosis accompanied by pulmonary embolism.

Thrombosis arising in active individuals at any age offers a very special problem. Some trifling strain or injury may lead to it, even a long airplane trip. Since there is seemingly little excuse for such an event (I have seen it arise "spontaneously" more than once in girls of eighteen to twenty), it may be supposed that the individual is thrombophilic, a matter not demonstrable as a rule by ordinary blood tests. In the older age group, pulmonary embolism, even repeated pulmonary embolism, may occur simulating angina pectoris or coronary disease. Before anticoagulants were available in the early 1930's, I treated all such patients^{8,9} by vein interruption. I now believe that early thrombosis, when the process has not yet invaded the femoral vein (the extent of the disease is much easier to recognize in ambulatory than bed patients) should be given anticoagulant therapy, preferably with dicumarol. I have even permitted one patient, a doctor, to be ambulatory under dicumarol treatment, since he was able to secure daily blood tests of the prothrombin level. For more chronic and advanced disease of this sort, vein interruption should be used, either superficial femoral vein ligation or, if the disease is clearly unilateral, ligation of the common iliac vein, an operation which I have previously described^{10,11} and will presently discuss. In connection with either of these procedures, blood studies, perhaps after DeTakat's¹² suggestion of a test reaction to heparin, are indicated; and should the blood appear thrombophilic, anticoagulant therapy may be combined with surgery during the few

days in which the patient is becoming fully ambulatory.

Thrombosis without pulmonary embolism recognized in patients recently subjected to major surgery, in those convalescent from such an illness as pneumonia and in many of those suffering from cardiac decompensation and from coronary occlusion, should receive anticoagulant therapy. I group these patients together since they are likely to offer the opportunity to use anticoagulants *for a limited time while the individual is returning to an active life*. If possible, I would exclude from this group patients of the bad risk sort unlikely to return soon to normal life and therefore persistently liable to thrombosis, as already explained. This is perhaps the ideal way to use anticoagulants as indicated by Bauer,¹³ Jorpes^{14,15} and the Swedish school in general.

Thrombosis accompanied by pulmonary embolism is preferably treated by vein interruption. Bilateral femoral vein ligation is to be used. These patients, in whom thrombosis is presumably well established, may already be very troublesome problems for anticoagulant therapy. Dosage will usually be difficult to establish and further embolism is likely to be fatal. It may also happen that ambulation must be delayed considerably in which case vein interruption will have its greatest authority. As a rule these are bad risk patients. In most instances of this sort, the thrombosis will clearly be present in the legs and can be regarded as bilateral, though its extent toward the heart may be very difficult to determine. Sometimes, however, there will be no way of excluding a pelvic origin for thrombosis as in many gynecologic and prostatic cases. Then the question will arise whether to explore both femoral veins and suck out such soft thrombus as may be found, or whether to admit that the process can be controlled surgically only by a vena caval ligation. If the femoral vein exploration is

used, it should probably be supported by anticoagulant treatment in fear of further immediate embolism from any thrombus left in the great iliac veins. Such anticoagulant treatment may also be indicated in support of vein interruption in cardiac cases because of uncertainty whether embolism is coming from the legs or from the right heart.

COMMON ILIAC VEIN LIGATION

When a chronic or recurrent thrombosis appears to be *unilateral*, as in a considerable number of instances of old thrombophlebitis and especially when embolism from such a process is proved or suspected, common iliac ligation^{10,11} offers very decided advantages. The operation is acknowledged to be more difficult than femoral vein ligation and requires a general anesthetic. Sometimes the vein is friable and dangerous to handle. But the collateral circulation is vastly more abundant than when the common femoral vein is interrupted. Indeed, one can be sure that the venous return will be improved by the procedure. Bancroft^{16,17} has made considerable use of it. In my own experience of fifteen such interruptions, further embolism has been prevented but the operation does not fully protect against an occasional recurrence of thrombosis. In only one case, however, has this been true.

VENA CAVAL INTERRUPTION

There is now available a number of reports of this procedure sufficient to assay its value and warn of its dangers. When serious embolism has occurred and especially when further embolism must be prevented at all costs, the operation offers the surest protection. Under these circumstances it should be preferred to a more peripheral interruption in the presence of an ascending bilateral thrombosis of the lower limbs. It may even be used (in the absence of cardiac

disease as a possible source) when the origin of embolism is merely presumed though not proved to be in the pelvis or lower limbs. But if a pelvic (uterine or ovarian) origin is suspected, the ovarian veins as well as the vena cava must be ligated (Collins, Jones and Nelson).¹⁸

To those, like Murray,⁵ who appear convinced that anticoagulant therapy will always control thrombosis and prevent fatal embolism, even after warning and after nearly fatal embolisms have already occurred, vena caval ligation must seem an unnecessary and dangerous surgical venture. But under the conditions outlined in the preceding paragraph, the operation in skilled hands is entirely reasonable and sometimes inevitable. Wider indications are noted by Moses¹⁹ and more recently by Veal, Hussey and Barnes.²⁰ The resulting collateral circulation may be accepted as satisfactory. As to the technical difficulty and danger of the operation, a general anesthetic is required and the vena cava should be approached in such a way as to secure a good anterior view of the great vessel. For any lateral branches encountered are fragile and may be torn by the manipulation required for ligation; in which case, hemorrhage is difficult to control and may well be fatal. Actually, the operation is less disturbing to the very ill patient than one might suppose—far less so than a transperitoneal procedure—so that its proper mortality can be neglected. The re-education of the return circulation requires care but does not offer a serious problem.

I myself regard the operation as a last resort when peripheral ligation or anticoagulant therapy or a combination of both, as sometimes happens, have failed to halt embolism. Even though several series of thirty or more cases have been published from various surgical clinics, the mortality which has followed the operation, though relatively low and mainly attributable to

underlying disease, suggests that the operation has been somewhat overdone.

TREATMENT OF THROMBOPHLEBITIS

The obstructive, often inflammatory phase of thrombosis requires treatment devoted to both venous occlusion and secondary vasospasm. Embolism is a very minor consideration but since an outspoken phlegmasia alba dolens in one leg may carry with it a quiet phlebothrombosis in the other, that aspect of the disease must not be neglected. I have already pointed out that vasoconstriction declares itself mainly in the peripheral arterioles and venules but may provoke, though rarely, a serious persistent spasm of the great artery of the limb, even violent enough in some cases to cause gangrene. Ochsner and deBaakey^{21,22} have shown how the inflammatory reaction in a segment of vein can call forth reflexes inducing such effects, and how profoundly sympathetic paralysis, even a temporary block with procaine, can favorably affect the state of the swollen painful limb. The vicious circle of venous irritation and reflex sympathetic constriction can actually be broken by emptying the obstructed vein or even by surgically exposing it for some distance, but lumbar sympathetic block, as first suggested by Leriche,²³ is the standard procedure.

Lumbar sympathetic procaine block may be secured by various technics. The main thing is that it should paralyze, if only for fifteen minutes, the lumbar sympathetic chain. Several blocks over a series of days may be required to secure maximal release but even a single one is often extraordinarily efficient. The leg visibly shrinks, the skin wrinkles, the bluish pallor changes to pinkness, comfort is produced and surface veins begin to fill. But because the second leg may be the source of an embolus-threatening process, and because the thrombophlebitis itself may rarely cause embolism, anti-

coagulant therapy should be used for a week or so, or a superficial femoral vein ligation done on the second leg.

It has been shown that in the early stage of phlegmasia alba dolens (first week) femoral exploration and thrombectomy will have much the same effect as sympathetic block and will greatly shorten the convalescence. If this operation is carried out, the opposite superficial femoral vein can be ligated at the same sitting. A very important contribution of this operation is a permanent interruption of the superficial femoral vein (distal to the profunda). For canalization of the thrombosed vein is so much the rule that serious back pressure and consequent venous congestion of the entire leg often follow healing of thrombophlebitis. Both Buxton and Coller^{24,25} and the writer²⁶ treated the late complications of thrombophlebitis surgically by sectioning the now valveless femoral and saphenous veins. It may be that interruption during the acute state will prevent much future venous stasis, edema and ulceration. Obviously, it should not be performed in the presence of a lymphangitis in the femoral chain of nodes. Nor should any surgical procedure cause neglect of the carefully controlled convalescence, particularly the re-education of the venous return by gradual use of the limb in dependency.

TREATMENT OF THROMBOEMBOLISM IN "MEDICAL" PATIENTS

In 1940, White²⁷ called attention to "pulmonary embolism and heart disease" and Hampton and Castleman²⁸ showed by combined roentgenologic and pathologic study at the Massachusetts General Hospital that 60 per cent of fatal embolism was of medical origin—chiefly cardiac—against 40 per cent of a surgical sort. Since then, this side of the subject has received considerable but not yet sufficient recognition. In the description given at the beginning of

this paper, the frequent imitation of coronary occlusion and angina by pulmonary embolism was indicated. But when genuine heart disease exists, particularly congestive failure associated with hypertensive or rheumatic disease or coronary occlusion, it may well happen that a complicating venous thrombosis in the lower limbs and embolism from that source decidedly increase the danger to the patient over and beyond that relating to the cardiac condition itself.

To simplify as far as possible the problem of preventing such thromboembolism, and of treating it when established, one will do well to make very broad rules for diagnosis and treatment, admitting that accurate diagnosis is unattainable and that treatment is based on probabilities. Thus, the majority of those confined to bed by heart disease and kept for many days in a reclining position, with the legs somewhat dependent, relaxed and engorged, will develop thrombosis in their lower limbs, though the terminal quality of much of this thrombosis has already been noted. Such thrombosis may cause pulmonary embolism at any time. The quieter the process, the greater the danger of embolism from it. Edema of the limbs will usually be present whether or not thrombosis exists. Therefore, local muscular signs and actual embolism offer the chief evidence for the diagnosis. Pulmonary infarction is indicated by thoracic pain, hemoptysis and, especially, shadows on the x-ray film. Actual proof that any episode of pulmonary infarction is of lower-limb rather than of cardiac origin may be wanting but the percentages very decidedly favor the legs.

The effectiveness of dicumarol in the treatment of certain types of heart disease has been demonstrated by Wright²⁹ who believes that this anticoagulant can be continued, with proper controls, for long periods. However, the uncertainties of response to this drug, particularly in respect

to its assimilation and its action when the liver and kidneys are damaged, indicate the usefulness of vein interruption, at least as an alternative.

It is a good rule then that if, in any instance of heart disease in which confinement to bed for more than a week is expected, embolism is believed to have occurred (from thrombosis clinically evident or presumed to be present in the lower limbs), both common femoral veins should be explored and ligated. When there are actual contraindications for the anticoagulants, such a rule may be counted imperative; otherwise it is a matter for professional experience and judgment to determine. Carloti, Hardy, Linton and White,³⁰ in a very informative and thoughtful communication to the American Heart Association, discuss surgical treatment by vein interruption, and I am permitted to indicate the nature of their results. Among 151 cases (1941 to 1945) of heart disease in whom a diagnosis of embolism or infarction was made by any of several methods, sixty patients were subjected to femoral vein section (bilateral since 1943). Seventeen deaths in the group subjected to operation give a mortality of 28.3 per cent, as opposed to 50.7 per cent in a control series of 213 cases. Thirteen failures to prevent embolism (clinical evidence of infarction after operation) included no massive fatal embolisms, and in eleven of the thirteen the superficial rather than the common femoral veins had been divided. The authors have since used only bilateral common femoral vein interruption. Their publication deserves careful study.

COMMENTS

It will have been noted that in presenting the prophylactic and definitive treatment of venous thrombosis in the lower limbs I have made few didactic statements, that I have indicated a personal preference for anticoagulant therapy under a number of

conditions and that I have suggested here and there the advisability of a combined chemicosurgical treatment. Venous thrombosis occurs in the home, in rather primitive hospitals and in well equipped and staffed urban institutions. Moreover, the clinical conditions under which thromboembolism presents itself are many—postoperative, post-traumatic, medical, obstetric—and the disease appears to vary from clinic to clinic, from country to country, and certainly from climate to climate. Until statistics from many sources and on a scale larger than are now available are brought forward to cover strictly comparable groups of patients, it will be impossible to assay the relative value of anticoagulant and surgical treatment. It is my impression at the moment that today's tendency is toward increased use of the anticoagulant drugs—they became available only several years after the value of a vein interruption had become known—with the significant reservation that their use calls for expert knowledge and routine study of the blood. Heparin or dicumarol are particularly indicated in the treatment of acute, single episodes of thromboembolism. Interruption of veins is advantageous when the causes of thromboembolism are persistent or recurrent, or when any further embolism must at all costs be prevented. Both systems, optimistic statements to the contrary notwithstanding, will score tragic failures as well as dramatic successes and clearer indications for treatment than those now available will be made known only gradually.

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Combined Staff Clinics

Smallpox

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. HARRY M. ROSE: Smallpox is a subject that usually receives little attention in this part of the world. This attitude seems mainly to be the result of the fact that smallpox has virtually disappeared from our communities, together with the common belief that the general level of immunity in our population, produced by prophylactic vaccination, is sufficiently high to prevent any serious recurrence of the disease. Recently, however, smallpox appeared again in New York City. The source of the infection and the circumstances of the outbreak that followed will form a part of this discussion and it will be apparent that a serious epidemic was averted, probably only by the prompt and resourceful measures of control employed by the New York City Department of Health. Although the actual number of cases of smallpox in this outbreak fortunately was small, the public was considerably alarmed and the medical profession was made to realize that the disease still presents many unsolved problems. It is the purpose of this clinic to discuss some of these problems and to summarize the current knowledge of smallpox in the light of our recent experience.

Dr. Kneeland will open the discussion with a consideration of the clinical aspects of smallpox.

DR. YALE KNEELAND, JR.: It is likely that the vast majority of this audience has never seen a patient with smallpox. Indeed, it is a disease to which most of us in normal circumstances never give a thought; we regard

ourselves and our own society as completely protected. At some time or other we have skimmed through a textbook description which we can remember but vaguely and we think of the disease—if at all—as something visited on the unenlightened peoples of the earth for their sins, something which can never possibly happen to us. Yet a recent issue of the *Army Medical Bulletin** reports twenty-six cases with twelve deaths occurring in presumably immune American troops in Korea; fifty-nine cases with eight deaths in our similarly protected army of occupation in Japan and a secondary epidemic (from this source) taking place in Seattle with forty cases, eight of them fatal. Recently we had the disease in New York.

My own credentials as a clinical lecturer on smallpox are not impressive. True, I have seen a great many cases. But I saw them all in one day, in a fever hospital in the Middle East. This sort of experience does not impart a deep appreciation of any disease as a whole. Nevertheless, it made an indelible impression and has caused me to read about smallpox with avidity.

Now I do not think that any of you should endeavor to memorize all the details of the disease but you can rightly be expected to do two things: to bear it in mind and to have enough schematic notion of what it is like to suspect its presence if it occurs. Let us, therefore, review the classical textbook description and then compare it with some recent experiences in the field. For this pur-

* *Bull. U. S. Army M. Dept.*, 5: 616, 1946.

pose it is convenient to have before our eyes a graphic representation of the typical behavior of smallpox, and I have borrowed an excellent diagram from Dr. Murray Cowie's article in Cecil's Textbook of Medicine to serve this purpose. (Fig. 1.) Be it remarked

and geography it will be confused with influenza, typhus, sand fly fever, dengue fever, malaria and a host of others that come readily to mind. During this stage occasional "prodromal rashes," petechial, morbilliform or scarlatiniform, are described but

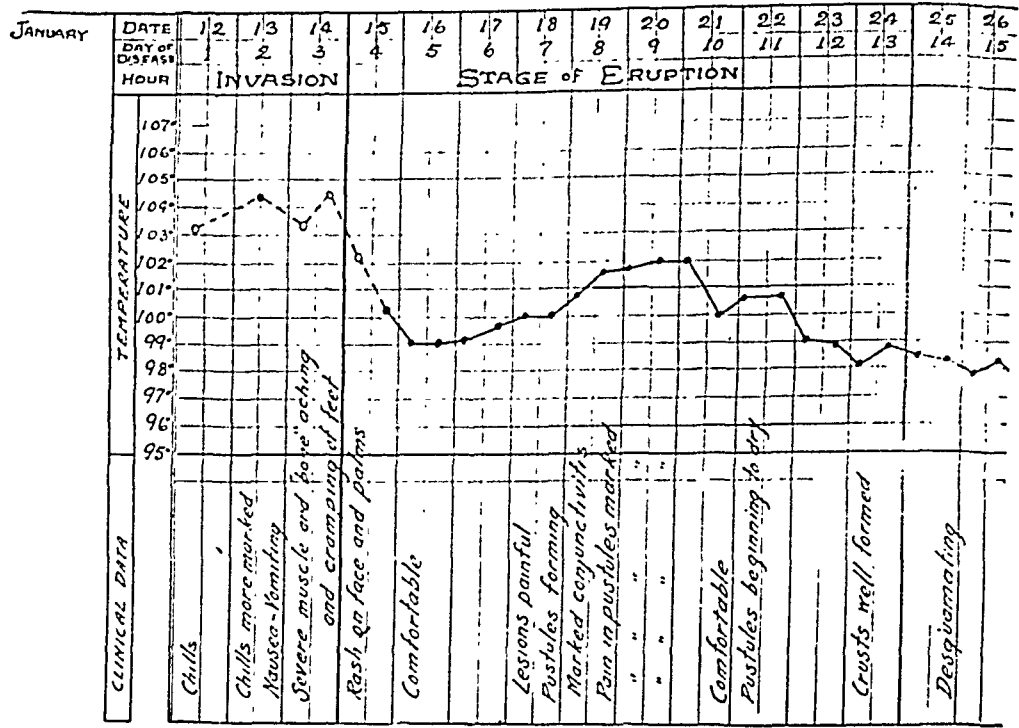


FIG. 1. Typical temperature curve from a case of smallpox, illustrating the secondary rise. (From Cecil's Textbook of Medicine.)

that unmodified virus and rickettsial diseases often tend to run remarkably close to form and smallpox is, therefore, the sort of disease in which a schematic chart is of the most value.

The incubation period is usually around twelve days, although very rarely it may be as long as twenty-one days. The disease begins abruptly and there ensues a period of invasion referred to as the "prodromal fever," which is characterized by chills, marked elevation of temperature, prostration, aching pains and vomiting. The total white count is usually within normal limits. Plainly then, there is nothing to distinguish smallpox at this stage from a variety of other acute infections. Depending on season

I do not think that we need burden our memory with these. On or about the fourth day, however, the characteristic exanthem of smallpox makes its appearance. It begins as a discrete macular rash but the macules rapidly become papular and have a shotty feel. Coincidentally with the rash the temperature falls and the patient feels better.

It is important to remember something about the distribution of the rash. Ordinarily, it appears first on the face; then it rapidly involves the upper extremities, with a preference for their distal portions; the trunk is next involved but usually less strikingly, and lastly the lower extremities become involved where most of the lesions are found below the knee. The palms and

soles are involved. The development of the exanthem is rapid and the phenomenon of "cropping" is not observed. That is to say, most of the lesions will be found in the same stage of development. This, together with the peripheral distribution, and the deeper, more indurated character of the lesion help to differentiate smallpox from varicella.

By about the sixth day of the disease the papules change into vesicles and tend to become umbilicated; by the eighth day their contents become turbid and the stage of pustulation has been reached. With this there is a secondary rise in temperature, an increase in constitutional reaction and often considerable local pain and pruritus. The lesions then begin to dry and crust. By the end of a fortnight the crusts are well formed and adherent and the fever has usually abated. Separation of the crusts and some desquamation then takes place; these processes are complete by the end of a month, leaving behind the permanent, pitted scars of the disease which are so familiar. Incidentally, there is also an enanthem, i.e., the eruption affects buccal, pharyngeal and other mucous membranes where extensive ulcerations may occur.

Smallpox epidemics in the past have varied considerably in severity, and the patient fatality rate of 15 to 45 per cent is a function of the relative predominance of the various clinical types which, in turn, is conditioned by the immunity of the population. The three main clinical types are the *discrete*, in which the lesions are separated and may be scanty and the mortality is very low, the *confluent* (Fig. 2, photograph I took in the Fever Hospital in Cairo) in which the fatality rate may approach 50 per cent, and the *hemorrhagic*. The latter is described as two types: "Purpura variolosa" or "black smallpox," in which there is early and extensive purpura and death is the rule; and "Variola hemorrhagica pustulosa" in which bleeding is limited to the lesions themselves



FIG. 2. Typical type of rash in confluent smallpox.

and the mortality is somewhat lower. Death may occur as a result of profound intoxication in severe smallpox, that is to say, owing to overwhelming virus infection itself. In untreated patients it may also occur from concomitant bronchopneumonia or septic complications.

So much for the schematic description of the disease, the salient features of which every physician should bear in mind. Let us turn now to a recent clinical experience with this historic disease. Illingworth and Oliver* have written an excellent description of one hundred patients with smallpox in the British military personnel in the Middle East. Of these, 96 per cent had been vaccinated, 70 per cent within two years of the epidemic. In other words it was the sort of population we might expect to deal with in an epidemic in this country. In spite of the vaccinations there were fourteen deaths. However, no doubt because of vaccination, they classified 54 per cent of their patients as "modified." I shall return to them a little later but first, in regard to *unmodified smallpox*, it is of interest that the authors found that it conformed closely to the classical description I have outlined above. They did note that headache was a more impressive symptom during the prodromal fever than backache (so frequently emphasized in the

* ILLINGWORTH, R. S. and OLIVER, W. A. *Lancet*, 2: 681, 1944.

literature) but in other respects the pattern ran true to form. The spleen was palpable in about half their patients and a leukocytosis early in the disease was associated with the hemorrhagic type. In non-hemorrhagic patients the count was usually around 8,000, with a tendency to rise late in the disease, at which time immature white cells and a reduction of platelets were noted.

The striking feature of the *modified cases* was the shortening of the prodromal fever. Sometimes these patients presented themselves with a vesicular eruption. Other patients might develop a vesicular rash after a day or two of fever, the vesicles then either maturing rapidly into the pustular form or aborting. It is quite obvious that in such patients the resemblance to chickenpox was very close indeed. The main clinical points of differentiation which the authors found of value were the presence of shotty nodules in the palms and the involvement of the palate and conjunctivae. These are characteristic of smallpox. Nevertheless, the two diseases may be impossible to separate on purely clinical grounds. Dr. Cox will probably tell you about the technic of serologic diagnosis and of virus identification. These methods unfortunately involve a great deal of time and, of course, the services of a first-rate virus laboratory. A quick test of some sort would be of obvious value in the field. Such a one has been described by Van Rooyen and Illingworth.* This consists in the demonstration of elementary bodies in specially stained smears from the lesions. Its great advantage lies in the fact that it can be done very quickly. Unfortunately, it too requires an experienced and highly trained technician but the results would appear to justify such training. Van Rooyen and Illingworth obtained positive results in forty-seven of fifty patients studied, in half of whom the clinical diag-

nosis had not yet been established, and there were no false positives.

While the diagnosis of typical florid smallpox is not difficult, I do not wish to leave in your minds the impression that it is an easy diagnosis to make in all cases. Far from it. I have already mentioned the difficulty in distinguishing it from varicella, particularly when the smallpox is "modified." The onset of chickenpox, the distribution of the eruption, its characteristic evolution, the fever curve, etc., differentiate it from unmodified smallpox. Many of these differences vanish when the smallpox occurs in a partially immune individual, and the remaining differences are too subtle for full clinical reliance. Apart from varicella there are other sources of confusion. I have indicated that there is nothing characteristic about the prodromal fever. In the early stages of the eruption it must be distinguished from scarlet fever and measles. When seen in the pustular stage it may be confused with any pustular dermatosis. To repeat, differential diagnosis is difficult and may be impossible but the first necessity is to realize that smallpox exists, to keep it in the back of one's mind and to remember some of its characteristic features.

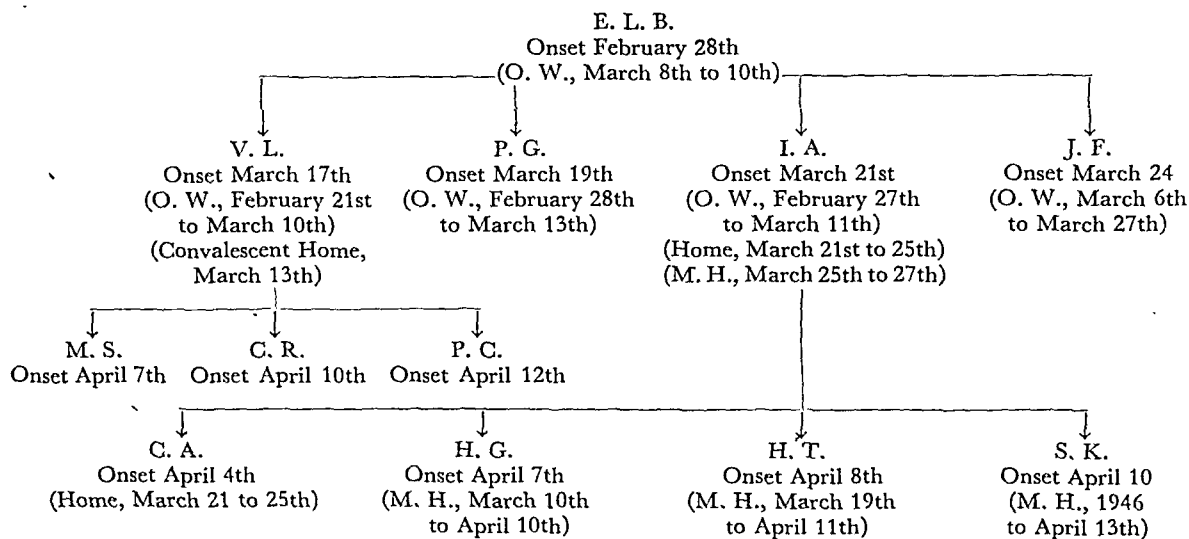
DR. ROSE: Dr. Kneeland has given a lucid account of the classical clinical features of smallpox as it occurs in the non-immune human subject. He has also pointed out that the classical picture of smallpox may be modified, often as the result of previous vaccination, and that the modified or atypical forms of the disease may be confused clinically with other acute exanthemata, notably chickenpox. We must constantly be alert to the possibility of smallpox in any patient whose signs and symptoms even remotely suggest the disease. Failure to recognize promptly and to isolate an atypical case of smallpox may lead to spread of the disease by extension to non-immune contacts, as illustrated by the

* VAN ROOYEN, C. E. and ILLINGWORTH, R. S. *Brit. M. J.*, 2: 526, 1944.

recent outbreak of smallpox in New York City. This was initiated by a patient in whom the clinical diagnosis was missed and who was not isolated in a communicable disease hospital until the tenth day of his illness, two days before death. The epi-

on February 25, 1947, and traveled by bus to New York City, with several short stops en route, arriving here on March 1st. According to his wife, who accompanied him, he became ill on February 28th. He registered at a midtown hotel on arrival

TABLE I
SPREAD OF SMALLPOX TO SECONDARY AND TERTIARY CONTACTS IN THE NEW YORK CITY OUTBREAK, 1947



O. W. Observation building—Communicable Disease Hospital
M. H. Municipal Hospital

demipologic features of the outbreak and the control measures employed for successfully limiting the spread of the disease will now be discussed by Dr. Morris Greenberg, Acting Director of the Bureau of Preventable Diseases, New York City Department of Health.

DR. MORRIS GREENBERG: Prior to the recent outbreak there had not been a case of smallpox developing in the city of New York for more than a generation. The last patient seen in the city was in 1939 when a person arrived with smallpox on a Portuguese boat. He was immediately isolated and no secondary cases occurred.

CASE I. The 1947 outbreak of smallpox could be traced back to the arrival in this city of an American business man, E. L. B., aged fifty, who had lived in Mexico for the past six or seven years. He left Mexico City

and transacted business until March 5th when he felt too sick to work. He was admitted to a municipal hospital on that day and remained there until March 8th when he was transferred to a communicable disease hospital. He was placed on the first floor of the observation building. He was then quite ill with pustular and hemorrhagic lesions all over his body. He died on March 10th. The possibility of smallpox was considered but a definite diagnosis was not made.

The man had been vaccinated in childhood. His wife was vaccinated in the communicable disease hospital.

The further spread of the disease is delineated in Table I, which summarizes the results of the epidemiologic studies in this outbreak. A more detailed analysis follows.

CASE II. On March 27th, I. A., a

Puerto Rican adult, aged twenty-six, was admitted to the communicable disease hospital. He had previously been admitted to the same hospital on February 27th for mumps and had been placed on the sixth floor of the observation building where he remained until March 11th, when he was discharged as cured. He worked until March 21st, when he became ill with headache and fever and went home. On March 25th, he was admitted to the dermatologic ward of a municipal hospital where he remained until March 27th. Then he was transferred to the communicable disease hospital and placed in isolation. He had a generalized papulo-vesiculo-pustular eruption. Smallpox was suspected and material from the lesions was sent to Dr. Smadel of the Army Medical School. Characteristic growth (on chick embryo) was obtained as well as a positive complement fixation reaction with antismallpox serum. The man had never been vaccinated. Attempts at vaccination in the hospital on two occasions gave no reactions.

CASE III. When I. A. was admitted to the isolation building on March 27th, two children were in isolation, P. G., a female, colored, aged twenty-two months, and J. F., male, Puerto Rican, aged two and one-half years. Neither had been vaccinated before. P. G. had been admitted to the same hospital on the first floor of the observation building, for croup, on February 26th and had remained until March 13th. On March 19th, she became ill at home, with fever and rash. Two days later she applied to a local clinic which sent her to the communicable disease hospital. She had a generalized papulovesicular eruption and was placed in isolation. The child did not appear very ill and the vesicular lesions, although present all over the body, including face, palms and soles, contained clear fluid. Material from the vesicles, examined at the same time as that of I. A., gave a characteristic growth

on chick embryo and a positive complement fixation reaction was obtained.

CASE IV. J. F., the other child, had been on the first floor of the observation building since March 6th for possible whooping cough. On March 24th he developed fever which continued for several days. On March 27th a papulovesicular eruption was seen and the child was transferred to the isolation building. The eruption was never widespread, although lesions were seen on face, palms and soles, and the child was not very sick. However, growth on chick embryo was obtained and also a positive complement fixation reaction. On two occasions this child as well as the previous child were vaccinated in the hospital after their lesions had appeared, but with no success.

CASE V. Still another child, who was a contact of the first child, developed smallpox. This was V. L., a colored male, aged four, who had never been vaccinated. He had been admitted to the third floor of the observation ward of the hospital for possible scarlet fever on February 20th and discharged as cured on March 10th. On March 13th he was admitted to a convalescent home upstate. He became ill with fever on March 17th and developed a rash which was diagnosed as smallpox. Three secondary cases occurred in the convalescent home; a white nurse, aged sixty, who had not been vaccinated since childhood; a colored boy, aged five, and a white girl, aged two. Neither of the children had ever been vaccinated.

CASE VI. I. A., Case II, had been sick at home from March 21st to March 25th. His wife, C. A., Puerto Rican, aged twenty-six, a primipara of seven months who had never been vaccinated, became ill on April 5th with backache, headache and fever. She was admitted the next day to the isolation building of the communicable disease hospital. At this time she had some maculopapules resembling rose spots on her chest

and one on her face. These developed and spread and within a few days she had a typical smallpox eruption. She had been vaccinated on April 4th and had a good take. She died on April 12th.

CASE VII. As stated above, case II had been admitted to the dermatologic ward of a municipal hospital on March 25th and remained there until March 27th. On the same ward at that time there were three patients who later developed smallpox. One of these was H. G., a colored man, aged forty-three, who had been on the ward under treatment for syphilis since March 10th. He had never been vaccinated. On April 7th he developed fever and headache and on April 10th a papular eruption appeared. He was transferred to the isolation building of the communicable disease hospital the same day. He developed severe confluent smallpox. He was vaccinated on April 9th and had a good take.

CASE VIII. The second man, H. T., white, aged fifty-seven, had never been vaccinated. He had been on the ward since March 19th with lymphoblastoma. He developed fever on April 8th and a rash was noted the same day. It was papular and later became vesicular, spreading until it involved the entire body. He was transferred to the isolation building of the communicable disease hospital on April 10th. He was vaccinated on April 9th and had a good take.

CASE IX. The third individual was S. K., white, aged sixty, who had been vaccinated about forty years before. He had been on the ward with pemphigus since August 6, 1946. He became ill with fever on April 10th and developed a papulovesicular rash on April 13th. He was transferred to the isolation building of the communicable disease hospital on the same day. He had generalized smallpox, complicated by pemphigus. He was vaccinated on April 9th and had a good take.

To recapitulate: Four individuals developed smallpox as a result of contact with an unrecognized case. Four other persons developed smallpox as a result of contact with one of the secondary cases and three others as a result of contact with another secondary case. Of the twelve individuals, nine had not been vaccinated before and three had been vaccinated in childhood, about forty years before. The diagnosis in all was confirmed by characteristic growth on chick embryo and a positive complement fixation reaction. The incubation periods varied from seven to sixteen days. There were two deaths, a mortality of 17 per cent.

STUDENT: I suppose there were many times during the outbreak when establishing or excluding the diagnosis of smallpox proved difficult. Could you tell us about that?

DR. GREENBERG: As Dr. Kneeland pointed out, the diagnosis of smallpox is not too difficult if the disease is suspected and if the clinical course and lesions are characteristic. At times during the recent outbreak, however, the differentiation between chickenpox and smallpox proved to be very difficult. Case IV, for instance, although never vaccinated, had no constitutional symptoms except fever for a few days and the rash was sparse and not pustular. It would undoubtedly have been diagnosed as chickenpox except that it occurred in the course of an outbreak of smallpox and confirmation of the diagnosis was received from the laboratory. On the other hand, during the course of the outbreak an adult Cuban was admitted with mild symptoms and a generalized vesiculopustular eruption. He had not been vaccinated since childhood. The rash was generalized and confluent and was profuse on the face, palms and soles, as well as on other parts of the body. The diagnosis shifted from chickenpox to smallpox and back as different physicians saw him. The diagnosis of chickenpox was finally agreed

to by all because of failure of laboratory confirmation of smallpox, because of the discrepancy between the profuseness of the rash and the mild constitutional symptoms and because on maturation of the pocks they were more like chickenpox than smallpox. Although it is true, as Leake points out, that the distribution of the rash is the most characteristic feature of smallpox, cases of chickenpox are occasionally seen which simulate the distribution of smallpox. The other features that differentiate the two diseases must then be taken into account in order to arrive at the proper diagnosis.

DR. A. RAYMOND DOCHERZ: Did this epidemiologic study throw any new light on the transmission of smallpox, especially in connection with air-borne transmission of the infectious agent?

DR. GREENBERG: The circumstances of the spread of smallpox within the communicable disease hospital suggest aerial transfer of droplet nuclei. Of the four secondary cases, two had been on the same floor in the observation building as the original patient, the third was on the third floor of the building and the fourth was on the sixth floor of the building. Since different personnel attended patients on the different floors and there was no interchange of linens or dishes, spread possibly occurred through aerial transfer of droplet nuclei.

DOCTOR: Is it because of the possibility of air-borne transmission that the Board of Health quarantines an entire building when a case of smallpox develops?

DR. GREENBERG: Yes, and the experience of this outbreak seems to vindicate the practice.

DR. ROSE: Dr. Greenberg, would you summarize the control measures undertaken to limit the spread of the disease.

DR. GREENBERG: Case II was admitted to the communicable disease hospital on March 27th, a tentative diagnosis of smallpox was made and on March 28th vac-

cination of all doctors, nurses, personnel and patients in the hospital was begun. Thereafter, all visitors to the hospital were vaccinated. As soon as a definite diagnosis of smallpox was made the following measures were taken:

Vaccination of Contacts. The building in the municipal hospital in which the dermatologic ward was located was quarantined and all patients and personnel vaccinated. Later the personnel and patients of the entire hospital were vaccinated. Also vaccinated were all personnel and patients who had visited the clinic on the day when Case III applied before going to the hospital. From the midtown hotel where the original patient resided lists of all guests registered there between March 1st and March 5th were obtained and all who were in the city were visited and vaccinated. Vaccination was also performed on all children who were exposed to the patients in the convalescent home and had returned to the city, as well as on the residents of the buildings in which Cases II and III lived.

Follow-up Visits. All contacts who had been discharged from the municipal and communicable disease hospitals and the convalescent home, all contacts who had lived in the midtown hotel and all residents of the buildings in which Cases II and III resided were visited daily by medical inspectors of the Department for a period of twenty-one days after the last exposure and examined for possible smallpox.

Notification. The United States Public Health Service was informed of the cases as they occurred and the names of contacts who lived outside of the city were forwarded for transmissal to the proper state health officers. The names of contacts who lived in New York State outside of the city were telephoned to the State Health Department, and lists of discharged patients from the convalescent home were received from the state authorities and followed-up. All hos-

pitals whose nurses affiliated with the communicable disease hospital were notified to vaccinate and to follow-up nurses who had left the hospital while the patients with smallpox were there.

Vaccination Campaign. The public was informed by the Commissioner of Health of the existence of smallpox in the city, using all means of communication—radio, press, lectures, etc. Vaccination was advised for those who had not been vaccinated recently. Physicians were offered vaccine free of charge for use in their practice, free clinics were opened in the central office and in all district health centers of the Department and arrangements were made with large employers of labor to have physicians of the Department visit their plants and offices and vaccinate all personnel.

The Department of Hospitals cooperated by opening free vaccination clinics in every municipal hospital and most of the voluntary hospitals opened clinics where vaccinations were performed free or for a small charge. Free clinics were later opened in all police precincts of the city, manned by physicians of the Department, and still later, vaccination was offered to school children of the city in their respective schools. In a period of three weeks more than 5,000,000 people were vaccinated.

DR. ROSE: Having considered the important clinical and epidemiologic features of smallpox, together with an intimate view of public health measures for its control, we shall now turn our attention to the etiologic agent, smallpox virus, and its relative, vaccinia virus. The discussion will be presented by Dr. Herald R. Cox, Director of the Section of Viral and Rickettsial Research, Lederle Laboratories.

DR. HERALD R. COX: The virus of smallpox is one of the larger of the agents classified as filterable viruses. It has a particle size averaging 0.2μ , according to indirect measurements made by filtration through

graded collodion membranes and by sedimentation in the ultracentrifuge, as well as by the direct measurement of particles photographed with the aid of the electron microscope. The essential particles or elementary bodies of the virus are therefore just within the limits of visibility using the ordinary compound microscope, and advantage may be taken of this fact in the diagnosis of the disease. As Dr. Kneeland brought out, if scrapings of the cutaneous lesions in the acute vesicular or pustular stage from a suspected case of smallpox are smeared on slides and stained by certain methods, such as those of Giemsa, Castaneda or Goodpasture, the finding of elementary bodies by a person experienced in their identification lends weight to the diagnosis. It should be noted, however, that failure to observe elementary bodies by such a procedure by no means excludes the diagnosis of smallpox. Moreover, the elementary bodies of smallpox virus are indistinguishable morphologically from those of vaccinia virus.

The multiplication of smallpox or of vaccinia virus in the tissues of the infected host is accompanied characteristically by the appearance of cellular inclusion bodies. Of these, the most typical is the Guarnieri body, which is a relatively large, round or oval structure, eosinophilic in its staining reaction and located in the cytoplasm. Acidophilic intranuclear inclusions are also seen in cells infected with smallpox virus, but not with vaccinia virus, a distinction of some importance from the standpoint of histopathologic diagnosis.

Two general methods are available for the specific diagnosis of smallpox in the laboratory, namely, the isolation and identification of the virus by inoculation of animals or chick embryos and the demonstration of specific antibodies to the virus in the blood of the patient. For isolating the virus from the cutaneous lesions the method

ordinarily employed is that first described by Paul. This consists of inoculating fluid or scrapings from the vesicular or pustular lesions onto the scarified cornea of a rabbit's eye. Two or three days after inoculation the cornea may appear slightly opaque and small vesicles or tiny shallow ulcers may be observed with the aid of a hand lens; painting the cornea with fluorescein is also useful in demonstrating their presence. The rabbit is sacrificed, the eye is enucleated and histologic sections of the cornea are prepared. Microscopic examination will reveal cellular proliferation and edema, together with areas of necrosis, and the pathognomonic Guarnieri bodies will be seen in the cytoplasm of some of the cells.

When the Paul test is positive the diagnosis is assured, but it must be pointed out that the test is negative in a considerable proportion of cases, especially when the disease is modified in character.

Another method for the specific demonstration of the virus in the cutaneous lesions without, however, actually isolating the agent consists in the performance of complement fixation or flocculation tests with antigens prepared from vesicles or pustules. Fluid from the vesicles or pustules is diluted with a little buffered saline, or crusts are ground up with the same diluent. These suspensions are then centrifuged and the supernatant fluids are used as the antigens. The antibody is serum from rabbits hyperimmunized by repeated injections of vaccinia virus. Flocculation tests are carried out by mixing dilutions of the antigen with dilutions of the antiserum and normal rabbit serum, incubating the mixtures and observing the appearance of a flocculent precipitate only in those tubes containing the antigen and the specific antibody. Using the same reagents, complement fixation tests may be performed in the usual manner, provided care is taken to dilute the antigen beyond the range of anticomplementary ac-

tivity and to dilute the antiserum sufficiently so that prozone inhibition is eliminated. Of these tests the complement fixation test is the more sensitive and reliable and is the one usually employed.

The laboratory diagnosis of smallpox may also be effected by the demonstration of specific antibodies developed in the patient's blood during the course of his illness and convalescence. The method is that of complement fixation, using the patient's serum as antibody and an antigen prepared from vaccinia virus which has been propagated either on the chorioallantoic membrane of the chick embryo or in mice by intracerebral inoculation. As Dr. Greenberg indicated, this type of test was employed successfully by Dr. Smadel at the Army Medical School, Washington, D. C., to establish the diagnosis of smallpox in some of the patients observed during the recent outbreak in New York City. In the hands of competent persons who are experienced with complement fixation tests using viral antigens, the procedure is reliable and of great diagnostic value but it should not be undertaken by those who are unfamiliar with the pitfalls that may be encountered.

The precise relationship of the virus of vaccinia to that of smallpox is still an unsettled problem. The chief point at issue is whether vaccine virus is actually a modified form of smallpox virus to which the cow and other animals, including humans, are susceptible; or whether the virus of vaccinia is an entity separate from but closely related to the virus of smallpox. The weight of evidence inclines toward the former view but is insufficient to be conclusive.

The method of prophylactic vaccination against smallpox differs little today from that employed originally by Jenner since it simply involves the transfer of vaccine virus, in the form of infected calf lymph, to the human subject. The technic of preparation of vaccine virus for immunization is of some

interest. Calves of either sex, with negative immunologic tests for tuberculosis and brucellosis and preferably with non-pigmented skins, are employed for the propagation of the virus. The skin of the flanks and abdomen is carefully shaved and is washed repeatedly with sterile soap and water. Scarification of the skin is then done in parallel lines about 1 cm. apart, superficially so that no blood is drawn. Passage vaccinia virus is rubbed thoroughly into the scarified areas. The animals are kept in stalls with special sanitary arrangements so that surface contamination of the inoculated areas is reduced to a minimum. After five or six days confluent vesicles have formed along the lines of scarification. The skin is now carefully cleansed again with soap and water and the vesicles and their contents are removed by scraping with a special curette; little or no blood is drawn if this is done correctly. The mixture of vesicular fluid and tissue scrapings is known as vaccine pulp. Following collection of the vaccine pulp the animals are sacrificed. The pulp is used only if no evidences of tuberculosis or brucellosis are found on postmortem examination.

The fresh vaccine pulp is mixed with an equal part of sterile glycerine, quickly frozen and stored in the frozen state. Under these conditions bacteria occurring in the fresh pulp gradually die. At intervals after freezing, therefore, samples are removed and examined for residual bacteria. When the bacterial count has reached a level of about five organisms per milliliter and if no pathogenic clostridia are present, the vaccine is tested for potency of the virus. This may be done either by inoculating non-immune human subjects or by titration into the skin of rabbits; in practice the latter method is usually employed.

It is of considerable importance that the vaccine virus tends to lose its potency if passaged serially in calves alone, but that the potency may be maintained if interval

transfers are made either in man or rabbit. In general, it is customary to transfer the virus intracutaneously to rabbits after every second or third passage in the calf and then to return the virus to the bovine host. In this manner the potency of the virus can be kept at a high level, apparently for an indefinite time.

When the glycerinized vaccine has been found to be satisfactory, as regards both bacterial contamination and virus potency, it is distributed for use. If kept at low temperatures, it will retain its potency for several months but if the environmental temperature is raised much above freezing the virus deteriorates within a week or two.

A number of attempts have been made to introduce a vaccine prepared from vaccinia virus, cultivated either in tissue cultures or in the developing chick embryo. The virus can be grown easily by either of these methods, which have the advantage that there is complete freedom from bacterial contamination. This type of vaccine has not found favor up to the present time, however, since there is some question that the virus may be altered antigenically under these conditions and thereby lose its ability to immunize effectively the susceptible human subject against smallpox. Nevertheless, this is not a closed issue and the possible development of an effective vaccine using vaccinia virus grown outside the animal host is one of the many important problems that remain to be solved in connection with smallpox.

DR. ROSE: Dr. Greenberg referred to the isolation of smallpox virus in chick embryos from patients in the New York City outbreak. Can you tell us something about this procedure as a method of diagnosis?

DR. COX: Smallpox virus may be readily cultivated in the developing chick embryo and many isolations of the virus directly from man have been made by this method. Material from pustules is inoculated into

the chorioallantoic membrane where growth of the virus is indicated by the appearance of pock-like lesions. Once the virus has been established in the chick embryo it may be maintained indefinitely by serial passage. The identity of the virus may be suspected by the character of the lesions produced on the chorioallantoic membrane and is confirmed by neutralization tests with specific antiserum.

The use of chick embryos for primary isolation of the virus is an excellent method for the specific laboratory identification of smallpox, although it must be said that a negative result does not exclude the diagnosis.

DR. ROSE: We come now to the important matter of vaccination. Dr. Kneeland, would you begin with a brief outline of the technic of vaccination.

DR. KNEELAND: First, it is of paramount importance to preserve the vaccine virus at icebox temperature and not to expose it to room temperature for any considerable time before use. The vaccine deteriorates rapidly on warming and this may account for many failures. The area to be vaccinated should be cleansed with soap and water and allowed to dry thoroughly. It is probably best not to use any other antiseptic, such as alcohol, for traces of it can inactivate the virus. At present the multiple pressure method is generally recommended and seems to have certain advantages. Lastly, it has been shown that the likelihood of secondary infection is diminished if the vaccination site is left uncovered.

A very good discussion of this topic will be found in an article by Leake* which is available in reprint form.

STUDENT: Why is so much emphasis put on not applying a tight covering to the site of vaccination?

DR. GREENBERG: Experience has shown that the hazard of infection is greater if a

tight covering is applied. Moreover, a dressing is likely to adhere to the secretion and thus interfere with the formation of a firm crust.

DR. ROSE: A tight covering favors the growth of anerobic bacteria which may be present on the skin at the time of vaccination. The tetanus bacillus is especially important in this respect and at one time tetanus was not an uncommon complication of vaccination. This has been rare in recent years.

DR. GREENBERG: Not one case of tetanus turned up following the recent mass vaccination.

DR. KNEELAND: Something should be said about the clinical features of vaccination, although this may seem superfluous to an audience, the majority of whom have been vaccinated recently. Those of you who have had a "primary take" must be thoroughly familiar with the sequence of events (Fig. 3)—how for three days or so nothing happened, then a papule appeared which turned into a vesicle at the end of a week and became pustular at the ninth or tenth day. At this time you may have noticed local and constitutional symptoms, including chills and fever. By the fourteenth day you were better and a firm crust covered the lesion. This train of events, as I said, characterizes the "primary take"; it occurs regularly in first vaccinations and in revaccinations when the individual's immunity has become low. When you have had this kind of response you may be pretty certain you are immune.

You may make the same assumption if you have had an "accelerated" or "vac-cinoid" type of reaction. Here the papule appears in a day or two, becomes vesicular and then pustular a couple of days later, to subside by the end of a week leaving a small scab. This indicates a positive reaction in a person whose immunity is fairly high, but I wish to caution you against placing

* LEAKE, J. P. Questions and Answers on Smallpox and Vaccination. *Public Health Rep.*, 60: 221, 1927.

too much confidence in the so-called "immediate" or "immune" response. By these terms is meant a papule which develops almost at once and subsides in a few days without going through the stages of vesiculation and pustulation. Quite true, this is

siderable numbers of people and getting a respectable number of primary takes, you can be relatively confident of the technic and potency of the vaccine virus. Then the finding of a few immune reactions in individuals with histories of fairly recent vac-

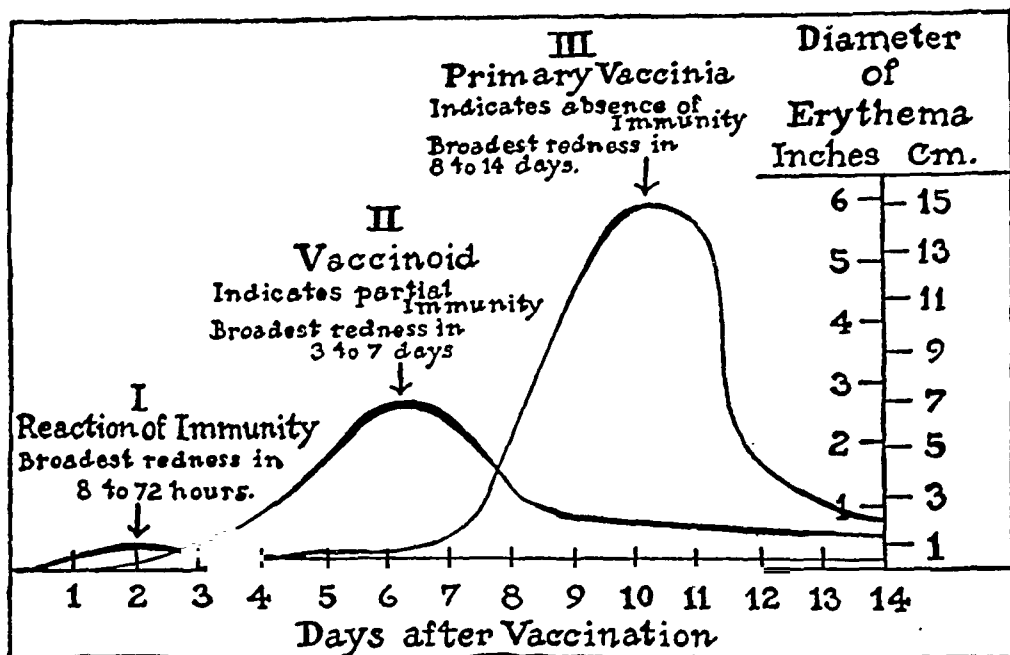


FIG. 3. The three types of reaction following vaccination; the height of the curves on different days indicates the diameter of the erythema. (From LEAKE, J. P. *Public Health Rep.*, 60: 221, 1927.)

the sort of reaction one expects in an individual whose immunity is of a high order but it also may mean no reaction at all, i.e., it may be the result of faulty technic of vaccination or improper handling of the virus. Emphasis has been placed on this by writers for the Army Medical Bulletin, who believe that the occurrence of smallpox in our "immune" troops may have been due in part to misinterpretation of the so-called accelerated or immune reaction. Lastly, I must urge you personally to examine all the people you vaccinate at appropriate intervals in order to evaluate the response.

DOCTOR: How do you deal with "immune reactions"?

DR. KNEELAND: That is a difficult question to answer. If you are vaccinating con-

tinuations should not be disturbing. On the other hand, if many immune reactions are obtained, particularly in patients who have not been vaccinated in years, this is cause for suspicion of either the technic or the lymph and calls for revaccination. If I were dealing with troops, let us say, who were about to enter an area where smallpox was endemic, I should be inclined to revaccinate at least once all those who showed an immune response. Let me emphasize again how important it is to examine repeatedly all individuals after vaccination who are at all likely to be exposed to the disease.

DR. HOWARD BRUENN: What are the contraindications to vaccination?

DR. GREENBERG: We advise against vaccination in the first trimester of preg-

nancy; ill effects in the offspring are not known to occur but in view of what has been discovered concerning the effects of German measles virus it is considered prudent to regard early pregnancy as a contraindication. Patients with generalized dermatoses and those with acute infectious diseases also should not be vaccinated.

DR. FREDERICK K. HEATH: A problem that arose during the outbreak concerned surgical procedures following vaccination. How long an interval after vaccination should elapse before operative procedures may be performed safely?

DR. GREENBERG: Vaccinia virus may be present in the blood for several weeks after vaccination. It would seem wise, therefore, to postpone elective operations for several weeks.

STUDENT: How often should vaccination be performed to furnish adequate immunity?

DR. ROSE: Vaccination should be repeated every five to ten years under ordinary circumstances, with the understanding that individuals vary widely in the rate at which immunity is lost. If, however, a person is to reside in any area where smallpox is endemic and severe, as in the Far East, then revaccination at yearly intervals is recommended.

DOCTOR: What about "false positive" serologic tests for syphilis following smallpox vaccination?

DR. ROSE: In 1940, Barnard observed that smallpox vaccination may be followed by the transient appearance of positive complement fixation and flocculation tests for syphilis in persons who are non-luetic. Since then a number of studies have amply confirmed this fact and have established the overall incidence at approximately 15 per cent. Rein and Ellsberg* have shown that positive tests develop most frequently following primary vaccinia, less frequently

after a "vaccinoid" reaction and least often after the so-called "immune" response to vaccination.

Positive serologic tests for syphilis appear one to two weeks after vaccination and usually disappear quickly within another two or three weeks but in some patients they may remain positive for several months. Fortunately, the reactions are mostly of low titer and will rarely be confused with the high titered reactions ordinarily encountered in patients with untreated syphilis, but this criterion alone cannot be relied upon to effect a distinction between the presence or absence of luetic infection. Whenever syphilis is suspected from the evidence of positive serologic tests the question of recent vaccination should be routinely included in the history.

DR. GREENBERG: Dr. Rosenthal has followed some of the persons vaccinated during the recent outbreak and he informs me that about 10 per cent of his series gave serologic reactions for syphilis which were positive in some degree.

DR. HEATH: One aspect of great practical importance has not yet been touched upon, the nature and incidence of postvaccinal encephalitis.

DR. ROSE: The nature of postvaccinal encephalitis or, more properly, encephalomyelitis, is not entirely clear. The disease is an acute meningo-encephalitis which ordinarily appears from seven to fourteen days following vaccination. It is a rare complication and has been found to occur, on the average, about once in every 100,000 persons vaccinated. However, in some series the incidence has been reported as high as 1 in 20,000.* Apparently the disease is observed most frequently in children following primary vaccination; it is much less common in both children and adults following revaccination.

The onset is usually abrupt and the

* MARSDEN, J. P. *Bull. Hyg.*, 21: 555, 1946.

* REIN, C. R. and ELLSBERG, E. S. *Am. J. Syph.*, 29: 303, 1945.

course may be characterized by headache, fever, vomiting, paralyses, coma and convulsions. The signs are commonly those of a diffuse cerebral involvement, although in some patients the predominant symptoms are those of cord involvement, including the anterior horns.

The pathologic changes are essentially those of an acute, widespread demyelination and they are similar to the lesions seen in patients with encephalomyelitis following measles, chickenpox or antirabic vaccination. The same type of encephalomyelitis also occurs in patients suffering from smallpox, regardless of antecedent vaccination, and the incidence there is about 1 in 2,000.

The mortality rate from postvaccinal encephalomyelitis is high and ranges from 30 to 60 per cent.

The etiology is still not definitely known. Attempts to isolate vaccinia virus and other neurotropic viruses from the central nervous tissue of fatal cases have been almost uniformly unsuccessful and it would therefore appear that the disease is not caused by the direct action of vaccinia virus or the activation of other latent viruses. However, another possibility is that the syndrome is caused by some form of sensitization or allergic response. The incubation period with adequate time for antibody formation, together with the failure to recover vaccinia virus, suggests this possibility. Moreover, in those cases that occur following revaccination the incubation period is shortened and the onset is accelerated, which may indicate an anamnestic type of immune response. Finally, it may be noted that an acute disseminated encephalomyelitis may be produced experimentally in monkeys by the injection of brain tissue combined with certain adjuvants. This experimental disease closely resembles postvaccinal encephalomyelitis both clinically and pathologically and is clearly the result of an immunologic phenomenon.

DR. HEATH: There has been much loose talk about postvaccinal encephalomyelitis following the recent mass vaccination in New York. Can you give us the facts, Dr. Greenberg?

DR. GREENBERG: We have been following a number of cases of individuals who have had symptoms resembling encephalomyelitis following their vaccination. We have also investigated deaths of all such individuals.

Fortunately, we have been able to obtain autopsies in all of the cases. At the present time we have records of five deaths in which encephalomyelitis was suspected of being the cause of death. One of these patients lived out of town. The brain was examined by two competent pathologists, neither of whom found any evidence of inflammatory lesions. A similar case occurred in New York City and the brain was examined by Dr. Rivers of the Rockefeller Institute. No inflammatory lesion was found. Two of the cases were examined by the Medical Examiner's Office and were found to have had tuberculous meningitis. The fifth death was also a medical examiner's case. Dr. Gonzales informs me that there were sufficient lesions of the circulatory system to account for the death. There was nothing found on gross pathologic examination of the brain but the sections have not yet been run.

Thus, up to the present, we have not had a single death that could be ascribed to encephalitis following vaccination.

SUMMARY

DR. HEATH: The recent outbreak of smallpox in New York City not only emphasized how casual is the acquaintance most physicians have with the disease but also clearly showed the many defects in our knowledge concerning it. On the other hand, the happy outcome of events furnished striking testimony to the efficiency of epidemiologic and public health measures when properly applied and serves as a

tribute to the New York City Board of Health.

The usual incubation period of variola is twelve days, although variations from five to twenty-one days are not unknown. The period of invasion follows, lasting three to four days, characterized by chills, fever, prostration, muscular aches, headache, nausea and vomiting. Rather suddenly, the macular eruption then appears on the face and distal upper extremities, accompanied by a decrease in the symptoms and fever. The rash progressively becomes papular, vesicular and pustular, terminating by crusting and desquamation in about two to four weeks. An ulcerating enanthem may accompany the exanthem. In fatal cases the ordinarily transient secondary fever appearing with pustulation remains to the end. In general, the mortality is higher the more marked the fever and the eruption, death resulting from overwhelming viral infection, sepsis or pneumonia. Smallpox modified by immunity resulting from vaccination may pursue an atypical abbreviated course and confusion with chickenpox may be unavoidable. During the invasive period of the disease, when a morbilliform or scarlatini-form rash may be present, measles or scarlet fever may be suspected; if no rash is present the disease may be indistinguishable from a variety of febrile conditions.

A variety of diagnostic procedures, all requiring expert technic, are available to aid in laboratory diagnosis. Material from the vesicles or pustules may be examined either by direct smear and search for elementary bodies or more specifically by growing the material on the rabbit cornea (Paul test) or chick embryo. Finally, complement fixation or flocculation technics may be used to demonstrate specific antigens in the lesions by titration with high titer rabbit antiserum, or the development of antibodies in the blood of the patient may be determined by the complement fixation

method using known vaccinia virus as antigen.

In connection with vaccination, emphasis is placed on using potent vaccine since potency lasts only a few months after preparation and decreases rapidly when the vaccine is stored above freezing temperatures. The dangers of bandaging are pointed out but no mention is made of the disability following leg vaccination, frequent and severe enough to disqualify this as a procedure of choice. The significance and characteristics of the primary and accelerated takes are noted; an immune type of reaction, unless it occurs in a recently vaccinated individual, may be due to poor vaccine or faulty technic and calls for revaccination. At this time, pregnancy in its first trimester, acute infectious disease and generalized skin disease are regarded as the only contraindications to vaccination. Elective surgery should be postponed following vaccination although urgent procedures have been performed without ill effect. The duration of immunity resulting from a successful vaccination varies with the individual. Vaccination should be repeated every five to ten years ordinarily and in endemic areas revaccination should be carried out at least annually.

An interesting complication of vaccination is a diffuse meningo-encephalitis bearing a mortality of from 30 to 60 per cent and possibly representing an allergic response in the central nervous system. As yet there is no evidence, except temporal, to suggest that this is a viral infection.

An account of the New York City outbreak discloses the hazards of wrong diagnosis and the rapid spread of the disease among non-immune subjects even though not in direct contact with the disease. The tremendous task of limiting such a potential epidemic and the measures used are detailed in the text. No more effective argument for compulsory vaccination can be advanced.

Clinico-pathologic Conference

Hypertension with Papilledema*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. S., was a thirty-nine year old machinist who entered the Barnes Hospital on November 28, 1946 complaining of headache, vomiting and blurring of vision. The family history was non-contributory. The patient had enjoyed generally good health. System review revealed that for several years his hearing had been gradually failing; one year before entry the patient had a penile lesion for which he received penicillin and arsenic treatment over a period of six months with apparent recovery. His diet had been adequate and his alcoholic intake was moderate.

In July, 1946, the patient developed pain and swelling of the knees, hands, wrists and ankles lasting about one month. The joints were said to have been painful and somewhat swollen but not red. There had been no evidence of preceding infection. Shortly after the onset of the arthritis the patient had ten or twelve episodes during which he suddenly lost consciousness. The attacks occurred while he was ambulatory as well as recumbent and lasted only several minutes. His arms and legs became stiff before an attack but as far as was known he had had no convulsions. After several weeks the attacks ceased and thereafter did not recur. The patient was advised by his physician to go to a spa and while there, another physician told him that he had tuberculosis, although at no time had he had any pulmonary symptoms. He was advised to go to Arizona

which he did; during his stay he had several episodes of cramping abdominal pain. He had no other gastrointestinal symptoms and he remembered no further details about this phase of his illness. Three weeks before entry to the hospital, he returned to his home in Illinois and soon thereafter began to have headaches of increasing severity, localized in the orbital and the temporal areas. The headaches were described as pulsating in character and they soon became constant. Two weeks prior to admission the patient began to vomit about three times a day although he did not complain of nausea. Vomiting persisted and he was able to take very little nourishment. Three days prior to entry his vision became blurred. The headaches and vomiting increased and he was referred to this hospital.

At the time of entry the physical examination revealed the temperature to be 37.3°C., pulse 85, respirations 16 and blood pressure 230/140. The patient appeared chronically ill and older than his stated age; he lay flat in bed holding his head and at times cried with pain. He answered questions only with great difficulty. The skin was sallow and dry. Several large, rubbery, discrete, non-tender lymph nodes were noted in the inguinal regions and a few shotty, axillary nodes were also palpable. Exophthalmos was noted. The pupils were round, regular and equal and reacted to light and accommodation. Examination of the fundi

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

revealed bilateral papilledema, many hemorrhages and exudates and marked arteriolar narrowing. The eardrums were thickened and somewhat retracted and hearing was impaired bilaterally. The teeth were carious. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular and the sounds were of good quality. The second aortic sound was accentuated. No murmurs were heard. The peripheral arteries were thickened and the temporal arteries were tortuous. Examination of the abdomen revealed no palpable organs or masses. A scar was noted on the glans penis. On rectal examination no abnormal masses were felt. Neurologic examination showed a peripheral right seventh nerve weakness; no other significant neurologic findings were described.

The laboratory studies were as follows: Blood count: red cells, 4,200,000; hemoglobin, 10.6 Gm.; white cells, 17,500; differential count: eosinophiles, 2 per cent; stab forms, 2 per cent; segmented forms, 62 per cent; lymphocytes, 32 per cent and monocytes, 2 per cent. Urinalysis: specific gravity, 1.015; albumin, 4+; sediment, 2 to 3 hyaline casts and 8 to 12 red cells per high power field. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 30 mg. per cent; total proteins, 4.6 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 1.8 Gm. per cent; calcium, 10.4 mg. per cent; phosphorus, 3.8 mg. per cent; chlorides, 89 meq. per liter and carbon dioxide combining power, 51.5 volumes per cent. Venous pressure: 100 mm. NaCl. Circulation time (decholin): 17 seconds. Electrocardiogram: indeterminate. Roentgenograms: "The bones of the skull appear thicker than usual. The sella turcica is within normal limits. No areas of destruction are visualized. The cardiac silhouette is within normal limits. The aorta is slightly lengthened. Minute deposits of calcification and a mini-

mal amount of fibrosis are seen in the apices of both lungs, but there is no evidence of active pulmonary disease. An open film of the urinary tract and intravenous pyelography are unsatisfactory."

Shortly after entrance to the hospital the patient was seen by a neurologic consultant who confirmed the findings described in the physical examination. He also noted a downward drift of the right arm on extension, indicating left cerebral localization. At his suggestion a lumbar puncture was performed. The initial pressure was 440 mm. of water and the final pressure 180 mm. of water. Ten cc. of clear fluid were removed. There were 3 cells. The protein was 123 mg. per cent and the Ayala index was 4.1. The patient exhibited no untoward reaction to the procedure.

The patient was somewhat obtunded and his condition was unchanged until the fifth hospital day when he had a generalized clonic convulsion, lasting several minutes. Repeat laboratory studies at that time showed the non-protein nitrogen to be 31 mg. per cent; the carbon dioxide combining power, 61 volumes per cent and the serum chlorides, 94 meq. per liter. Urinalysis again showed albuminuria and the sediment contained occasional hyaline casts and a few red cells per high power field. The patient was given large amounts of fluid daily and passed urine of low specific gravity. One week following entry he was noted to have developed bilateral hydrothorax and sacral edema. At that time his red blood count was 3,570,000, the white count, 14,000. The differential count showed a slight shift to the left.

On the tenth hospital day the patient had another generalized convulsion lasting several minutes. For twenty-four hours previously he had complained of increasing headaches; nausea and vomiting, which had been persistent throughout his hospital stay, had increased. For the convulsion he was

given 20 cc. of 25 per cent magnesium sulfate intravenously. His condition became progressively worse and he died on December 8, 1946, the eleventh hospital day. During the period of hospitalization his temperature at no time had risen above 37.5°C. His pulse had varied between 110 and 130 and his blood pressure averaged 210/120.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Whether or not it will be possible to fit all of the symptoms with which this patient was afflicted into a single clinical picture is problematical. Among other things he complained of arthritis, convulsions, abdominal pain, headaches and blurred vision. On physical examination the most conspicuous findings were those related to the vascular system, particularly the diastolic hypertension. Dr. Schroeder, would you care to suggest what type of hypertension this may have represented?

DR. HENRY A. SCHROEDER: The problem here is difficult, for there is no history of hypertension prior to the patient's admission to the hospital, therefore, it is not clear whether this was an acute or chronic phenomenon. At the time of entry he exhibited the syndrome called malignant hypertension which is characterized by a high diastolic blood pressure, cardiac enlargement, retinopathy, elevated non-protein nitrogen and abnormalities in the urine, such as albuminuria and hematuria. The fact that the patient's heart was not enlarged indicates that the hypertension may have been relatively acute in onset.

DR. ALEXANDER: It was noted in the physical findings that the patient had thickening of the peripheral arteries and tortuosity of the temporal vessels. How long must hypertension be present in order to produce such changes?

DR. SCHROEDER: It takes a relatively long

time. When peripheral arteries are described as being thickened, it is not always clear as to whether the examiner means a "rubbery" thickening, such as is seen in hypertrophy of the muscular coat in longstanding elevation of the diastolic pressure, or whether the thickening is of the "egg shell" variety which is common in arteriosclerosis. The tortuosity described in the temporal vessels could be either, but is more likely arteriosclerotic.

DR. ALEXANDER: On the x-ray film of the chest the aorta appeared somewhat lengthened. Do you believe that this finding is evidence of hypertension or more than several months' duration?

DR. SCHROEDER: I do not think that one can say. Aortic lengthening may be due to hypertension or it may be due to arteriosclerosis. All of the findings described, with the exception of those in the fundi, could be explained by arteriosclerosis alone.

DR. ALEXANDER: Dr. Moore, do you know how long it would take for sufficient hyperplasia of the peripheral vessels to give rise to thickening or lengthening?

DR. ROBERT A. MOORE: I know of no studies that offer an answer to that question. I think it can be said, however, that if the disease process existed fully developed for a year, there would certainly be anatomic changes. Whether over a much shorter period similar changes could arise, I do not know.

DR. ALEXANDER: Dr. Massie, the cardiac examination was rather unimpressive despite the marked hypertension. How long do you believe it would take for hypertension of the degree recorded here to cause changes in cardiac size?

DR. EDWARD MASSIE: There is considerable individual variation in cardiac response to hypertension and I do not believe that a definite answer can be given to your question.

DR. SCHROEDER: I believe that it is possi-

ble for hypertrophy to be present without dilatation; in such an instance the heart size might appear normal on x-ray.

DR. ALEXANDER: I think that we can consider that this man had malignant nephrosclerosis. Dr. Levy, do you believe that he may also have had a brain tumor?

DR. IRWIN LEVY: Possibly.

DR. ALEXANDER: Some years ago, before malignant hypertension was established as a clinical entity, hypertensive patients with the presenting complaints of severe headache and papilledema were often erroneously thought to have a brain tumor and craniotomy was not infrequently performed. Such confusion can be understood when one considers that the eye ground changes may be somewhat similar and there may indeed be focal neurologic signs. Dr. Schroeder, this patient's spinal fluid pressure was elevated. In malignant nephrosclerosis is a high spinal fluid pressure common and if so, what is the mechanism?

DR. SCHROEDER: It is usually thought to be due to cerebral edema.

DR. ALEXANDER: Is the protein of 123 mg. per cent compatible with cerebral edema?

DR. LEVY: I think that it is more in keeping with brain tumor than with malignant hypertension and cerebral edema *per se*.

DR. ALEXANDER: The headaches, retinal changes and increased spinal fluid pressure are all consistent with the diagnosis of brain tumor, are they not?

DR. LEVY: Yes.

DR. ALEXANDER: Against the diagnosis of brain tumor is the marked degree of renal involvement evidenced by albuminuria and hematuria. Unless the hypertension had been present for some time it would be difficult to explain the renal findings. On the other hand, the high spinal fluid protein is not in keeping with malignant hypertension. Dr. Wood, do you care to comment?

DR. W. BARRY WOOD, JR.: I do not be-

lieve that the renal changes can be explained on the basis of a brain tumor and I think another possibility, other than nephrosclerosis, should be considered. This patient may have had periarteritis nodosa which would have accounted for his initial arthritis, for the attacks of abdominal cramping and for the terminal picture of advanced renal disease. Furthermore, arterial lesions in the central nervous system could have given rise to the elevated spinal fluid protein.

DR. ALEXANDER: I agree that an excellent argument can be made in favor of periarteritis nodosa.

DR. WOOD: Dr. Carl V. Moore saw this patient on the ward. His first diagnosis was malignant nephrosclerosis but he suggested periarteritis nodosa as an alternate possibility.

DR. MASSIE: Is a six-months' history rather short for periarteritis nodosa?

DR. ALEXANDER: I do not think so. I am somewhat disturbed, however, by the absence of fever.

DR. WOOD: In most of the patients with periarteritis nodosa whom I have seen there has been fever. We should mention, however, that this patient did have a leukocytosis, which favors periarteritis nodosa over either malignant nephrosclerosis or brain tumor.

DR. ALEXANDER: Yes, a leukocytosis is very characteristic. Had there been fever the clinical picture would have been perfect for periarteritis nodosa. Yet, this disease has many variants, therefore, the absence of fever does not invalidate the diagnosis.

DR. WOOD: It is, of course, entirely possible that prior to his entry to the hospital, with some of his other episodes, the patient may have had an associated rise in temperature.

DR. ALEXANDER: Dr. Schroeder, would you comment further on the renal lesion of malignant nephrosclerosis?

DR. SCHROEDER: If the patient had malignant nephrosclerosis, one would expect to find arteriolitis involving the renal arterioles.

DR. ALEXANDER: Are not those lesions necrotizing?

DR. SCHROEDER: Yes, the necrotizing arteriolitis distinguishes the lesion of malignant nephrosclerosis.

DR. ALEXANDER: I believe that the lesions of periarteritis nodosa likewise are characterized by necrotizing panarteritis. I should like to ask Dr. Robert Moore whether in periarteritis nodosa the small arteries are involved?

DR. R. A. MOORE: In polyarteritis the disease process involves the medium-sized and large arteries rather than the arterioles. In my opinion the lesion in both lupus erythematosus and polyarteritis differs fundamentally from the lesion of malignant nephrosclerosis. In the first two, the process is predominantly inflammatory, whereas in the latter necrosis is characteristic. There is practically no reaction of an inflammatory character seen in malignant nephrosclerosis.

DR. SHERWOOD MOORE: Would you comment on the exophthalmos described in the physical examination.

DR. ALEXANDER: I believe that in extreme hypertension, exophthalmos has been described.

DR. PALMER H. FUTCHER: Dr. Warfield T. Longcope used to point out patients with chronic nephritis and hypertension who exhibited exophthalmos.

DR. WOOD: In this connection, mention should be made of the so-called "uremic stare," described some years ago by Hanes. Patients with uremia may indeed have extreme exophthalmos, suggesting a diagnosis of exophthalmic goiter. The patient under discussion today, however, did not have significant nitrogen retention.

DR. ALEXANDER: This patient during his hospital course developed bilateral pleural effusion and sacral edema. Dr. Massie, do

you believe that these features were cardiac in origin?

DR. MASSIE: The physiologic tests of cardiac function were all within normal limits but I see no other explanation for the edema; I do not believe that the serum albumin was low enough to cause edema.

DR. ALEXANDER: Dr. Futcher, how do you explain the low serum chloride?

DR. FUTCHER: Two possible reasons for hypochloremia come to mind. In the first place, the patient vomited considerably and in the second place, he may have had so-called "salt-losing nephritis."

DR. ALEXANDER: Do you wish to comment on the edema?

DR. FUTCHER: The serum albumin was somewhat below normal values and it is conceivable that that, plus a minimal degree of heart failure, may have been responsible. It is also true that patients with arterial diseases develop pleural effusion apparently as a result of inflammatory changes. The patient did not complain, however, of pleurisy.

DR. SAMUEL C. BUKANTZ: Dr. Alexander, would you care to comment on the possible relationship between the antibiotic therapy and the development of possible periarteritis nodosa six months later. The patient received penicillin shortly before his first symptoms appeared.

DR. ALEXANDER: I think your suggestion is an interesting one but as yet, no one has described periarteritis resulting from hypersensitivity to penicillin. The patient was also given arsenic but I doubt whether that compound could have initiated the process.

DR. FUTCHER: Returning to the possibility of a brain tumor, I wonder if Dr. Levy would tell us where this tumor may have been located.

DR. LEVY: I could not localize it any more than to say that it was in the left hemisphere.

DR. KEITH S. WILSON: May the patient have had a gumma of the brain?

DR. VIRGIL C. SCOTT: I believe that the time interval for the development of a gumma is too short.

DR. ALEXANDER: Could the lesion have been a tuberculoma?

DR. LEVY: I think that is possible. If I had to pick out a single neurologic lesion however, on the basis of a short history with seizures, I would suggest glioblastoma multiforme.

DR. ALEXANDER: In summary, the diagnoses of malignant nephrosclerosis, periarteritis nodosa and brain tumor have been suggested as an explanation of this patient's illness. The consensus of the opinion of the staff seems to favor a diagnosis of periarteritis nodosa. Are there other questions?

STUDENT: Would Dr. Massie comment on the tachycardia?

DR. MASSIE: I believe the tachycardia was merely a reflection of the terminal illness.

Clinical Diagnosis: Periarteritis nodosa.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: At the time of autopsy external inspection of the body revealed no abnormalities. The right thorax contained 700 cc. of clear, straw-colored fluid and 100 cc. of similar fluid were present on the left side. The heart weighed 430 Gm. In the lungs there were calcified fibrous scars at both apices and a calcified nodule in the right lower lobe. Four hundred cc. of fluid were present in the peritoneal cavity. The liver showed several small, depressed, purple areas immediately beneath the capsule. On cut surface these were red and soft. The cystic artery was readily palpable throughout its course over the gallbladder. The hepatic, splenic and mesenteric arteries were not remarkable. The most interesting findings were in the kidneys. They were slightly reduced in size, weighing 140 and 130 Gm., respectively. The external surface



FIG. 1. Photograph of kidney showing irregular nodularity.

showed marked irregular nodularity with large islands of elevated yellow tissue cut off by depressed, grayish-red, firm foci. On cut surface the depressed red areas extended throughout the width of the cortex but not into the medullary zone. The interlobar and arcuate arteries were unusually thickened. Examination of the bladder showed ecchymoses and petechiae in the mucosa. The brain showed flattening of the gyri with partial obliteration of the sulci. Multiple coronal sections revealed no additional anatomic changes.

DR. R. A. MOORE: The gross examination of the kidneys (Fig. 1) showed characteristic changes in the surface with large nodules, irregular in size and shape, yellow in color, retaining the structure of the renal cortex. Between the nodules there were depressed areas, irregular in outline, red or reddish-gray in color, obviously composed of fibrous tissue. Throughout the renal substance, particularly in the elevated areas, petechiae in varying sizes up to 1 mm. in diameter were seen. The large flat U-shaped scars suggested chronic pyelonephritis. The only point against that diagnosis was the fact that the changes in the renal pelvis were not as marked as those in the renal parenchyma. The character of the preserved tissue indicated that the patient had some degree of arteriolar nephrosclerosis which had gone

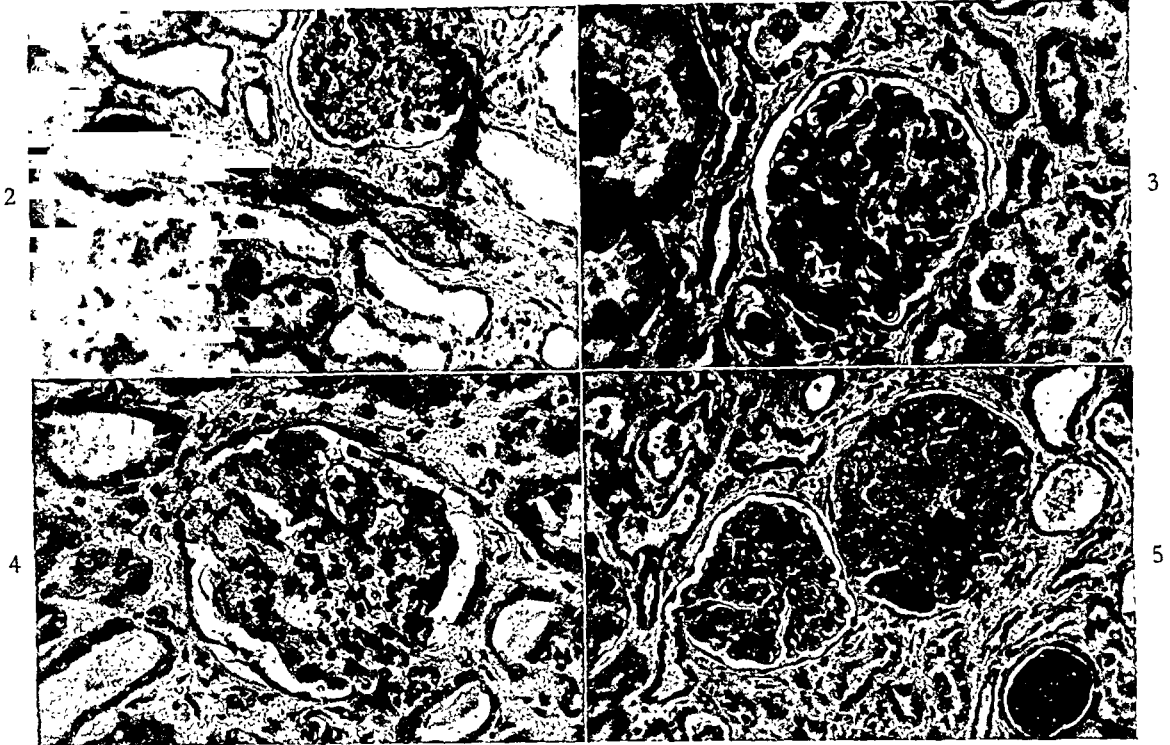


FIG. 2. Microscopic section through one of the elevated nodules of the kidney.

FIG. 3. Section of the kidney showing a glomerulus. Note necrosis of the entering arteriole.

FIG. 4. Another section through the kidney showing a glomerular adhesion. Note the epithelium of the convoluted tubule opposite the entering arteriole. It represents a portion of the juxta-glomerular apparatus.

FIG. 5. Section of the kidney showing the changes of infarction of a glomerulus.

on to the malignant phase. Accordingly, on the basis of the gross observations, diagnoses of chronic pyelonephritis and arteriolar nephrosclerosis with petechiae were made.

Let us now turn to the microscopic findings. Figure 2 shows a characteristic section through one of the elevated nodules; the renal substance is moderately well preserved. There is an increase in connective tissue, great thickening of the arteries and arterioles and necrosis in a part or all of the walls of the thickened arterioles with very slight cellular infiltration. These lesions are characteristic of arteriolar disease but they are not uniform. When individual vessels were reconstructed by step sections it was found that there were plaque-like lesions either in the media or intima.

In Figure 3 there is a glomerulus which shows necrosis of the entering arteriole.

There are thrombi in the lumen of the primary capillary branches of that vessel. There are also degenerative changes in the renal tubules and very slight increase in connective tissue with edema of the interstitial substance of the kidney. In another glomerulus (Fig. 4) a glomerular adhesion may be seen and there is a change in the cellular type of epithelium lining Bowman's capsule. It is well to point out that in the distal convoluted tubule the epithelium directly opposite the entering arteriole is very tall and represents a part of the juxta-glomerular apparatus, about which there has been much discussion in the past ten years. In other glomeruli dilatation of the capillaries with thickening of the basement membrane was seen. Some of the glomeruli show an increase in the number of nuclei and an occasional glomerulus has undergone

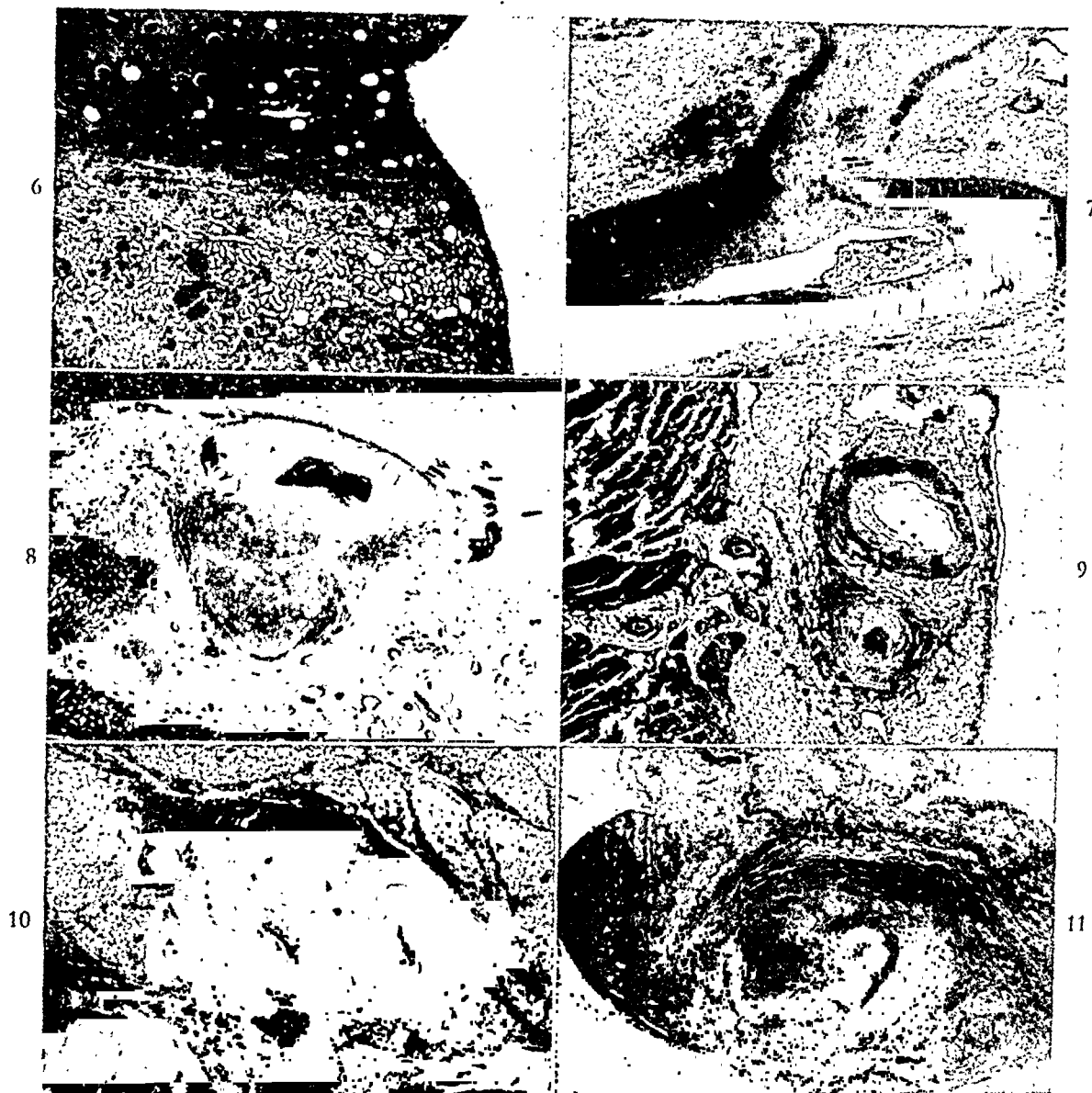


FIG. 6. Low power view of one of the scars of the kidney.

FIG. 7. Section through a branch of the renal artery. Note the intimal thickening particularly.

FIG. 8. Section of another artery. Note that the media is destroyed and that there is a fibrotic bulge which represents an obliterated aneurysm.

FIG. 9. Section through two coronary arteries. One shows intimal thickening while in the other there is complete obliteration of the lumen.

FIG. 10. Section showing small arteries in the capsule of the adrenal gland. Note obliteration of the lumens and marked adventitial fibrosis.

FIG. 11. Section of the cystic artery showing almost complete destruction of the muscularis.

total infarction. (Fig. 5.) Such a phenomenon is the anatomic change responsible for the gross observation of petechiae as well as the clinical observation of red blood cells in the urine.

From these observations it can be con-

cluded that this patient had the malignant phase of arteriolar nephrosclerosis. Now to return to the scars which were noted in the kidneys. Figure 6 shows a low power view of one of these scars which could represent chronic pyelonephritis, as was thought on

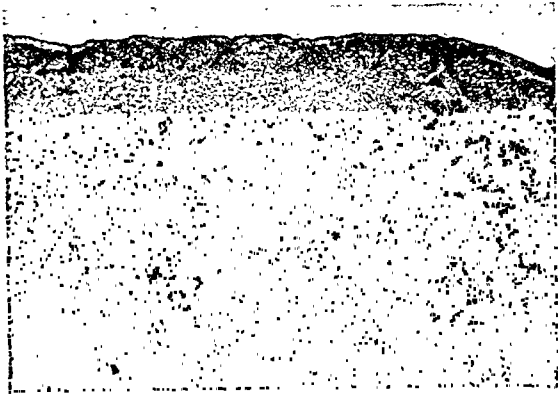


FIG. 12. Section of the liver showing an area of infarction.

the basis of the gross observations, or vascular occlusion of some type. At the base of some of the scars interesting vascular lesions are seen. If one examines a branch of the renal artery as it emerges at the pelvic region (Fig. 7), it is seen that there is tremendous thickening of the intima with a basophilic type of loose collagenous tissue. The adventitial tissue is densely fibrotic and contains a great deal of collagen. There is irregular thinning of the media as though it had been destroyed. In Figure 8, an artery is shown in which the media has completely disappeared and a local bulge which is densely fibrotic can be seen. It represents an aneurysm which has obliterated itself with periadventitial inflammation. In none of these sections is there evidence of active inflammation, but rather there is proliferation of fibroblastic tissue filling the lumen, dense collagenous tissue in the adventitia and focal destruction of the media at many points.

The heart was enlarged, weighing 430 Gm. In Fig. 9, one of the coronary arteries shows intimal thickening and in the other, there is complete obliteration of the lumen with destruction of the media, again with surrounding fibrous tissue. There is no cellular infiltration. In the small arteries in the capsule of the adrenal gland (Fig. 10) the amount of adventitial fibrosis is striking as is the almost complete obliteration of their

lumens. The involvement is entirely irregular in distribution with focal lesions producing nodules which extend into the lumens. Again, there is no cellular infiltration except for occasional lymphocytes and mononuclear cells. In Figure 11 a section of the cystic artery is shown; this vessel was actually palpable at the time of autopsy. The muscularis was almost totally destroyed. Under greater magnification, proliferating fibroblasts in a loose stroma of swollen, markedly eosinophilic collagen were seen. In other words, the lesion represented fibrinoid change. In the liver, (Fig. 12) there is an infarct with much of the liver substance destroyed. Hyaline subintimal thickening of the small arteries is present. Similar changes were seen in groups of arterioles in the intestine.

To summarize these observations it is apparent that our diagnosis is healing polyarteritis nodosa. All of the anatomic changes of polyarteritis nodosa are present, particularly in the cystic artery, and also in the renal and coronary arteries. Characteristically, there is destruction of the media and aneurysmal dilatation at the point of destruction with surrounding dense fibrosis.

In reconstructing the course of the patient's illness, six months before entry to the hospital he may well have developed the lesions of polyarteritis nodosa involving the intrarenal arteries, probably with associated hypertension. During the intervening six months the arterioles throughout the body, especially those in the kidneys, exhibited sclerosing changes and finally during the last few weeks of life, the malignant phase of nephrosclerosis began and there was acute necrosis of the arterioles. It could be argued, however, that the patient originally had hypertension and developed polyarteritis later. I do not believe that there is sufficient anatomic evidence to decide whether the polyarteritis or the hypertension came first. I would like to believe that

polyarteritis was the initial lesion and that all the arteriolar lesions were secondary. The only evidence which I can cite in support of my view is that the necrotizing lesions in the kidney were most prominent and confined principally to that part of the kidney that did not have its blood supply seriously impaired. It is very difficult to find necrotizing lesions in the arterioles of the scars in the renal cortex.

The patient had bilateral apical tuberculosis with calcification. As Dr. Johnson has stated, the brain, aside from the finding of edema, was without abnormality and there was no evidence of syphilis.

DR. ALEXANDER: Is it not possible that the absence of fever was due to the fact that

the lesions seen here were healing? It seems very likely that fever in periarteritis nodosa may be more common when there is active inflammation about the vessels.

DR. R. A. MOORE: We made numerous sections in an attempt to find acute periarteritic lesions but none were seen.

Final Anatomic Diagnoses: Polyarteritis nodosa, healing, involving vessels of the kidney, gallbladder, liver, heart and mediastinum; infarcts in the right lobe of the liver; arteriolar nephrosclerosis with necrosis of arterioles; arteriolar sclerosis, generalized, with minimal necrosis of arterioles; hydrothorax, bilateral; hypertrophy and dilatation of the heart; hydroperitoneum and edema of the brain.

Editorial

Significance of Psychosomatic Medicine

THE present vogue of psychosomatic medicine is in large part attributable to two rather separate factors. One is the development of methods by which the physical components of emotions may be objectively evaluated, and the other is an increasing realization of the limitations of prevalent scientific procedures in the understanding and management of illness which is dependent upon emotional disturbances. Interest in the subject has been so stimulated that psychosomatic medicine now threatens to become still another specialty in the already alarmingly segmented medical effort.

Although the clinical importance of emotional reactions has long been recognized, preoccupation of physicians with physical and chemical abnormalities in disease has left little time for inquiry concerning their precise effects on the function and structure of the body. It is only in recent years that systematic study has been attempted by methods which permit objective measurement and evaluation. The observations of Wolf and Wolff¹ upon the behavior of the stomach during emotional stress opened the way to a new approach in the field of clinical investigation. They demonstrated that embarrassment and resentment, long known

to cause blushing of the face, simultaneously produced flushing, hyperemia and increased acid secretion in the normal stomach and that continuation or frequent repetition of the emotional reaction caused erosions of the gastric mucosa with symptoms which were indistinguishable from those of peptic ulcer. Of equal significance were their observations that in the same individual fear and dread were accompanied by blanching of the gastric mucosa with diminution or a temporarily complete absence of gastric secretion, with loss of appetite and disgust for food. Later studies by Wolff, Holmes, Goodell and Wolf² have shown that in the normal nasal mucosa, resentment and embarrassment produce hyperemia and excessive secretion while fear results in pallor and dryness. Observations by Almy and Tulin³ have shown similar reactions of the normal colon under the stress of pain and emotion.

There is little reason to suppose that the response to emotion of other tissues and organs is less significant. The literature is replete with evidence indicating the participation of the heart, the peripheral circu-

² WOLFF, H. G., HOLMES, T. H., GOODELL, H. and WOLF, S. Life situations, emotions and nasal disease. Changes in nasal function associated with varying emotional states and life situations. *Tr. A. Am. Physicians*, 59: 88, 1946.

³ ALMY, T. P. and TULIN, M. Alterations in colonic function in man under stress. Experimental production of changes simulating the "irritable colon." *Gastroenterology*, 8: 616, 1947.

¹ WOLF, STEWART and WOLFF, HAROLD G. Human Gastric Function. New York, 1943. Oxford University Press.

lation and the kidneys. It is now generally recognized that such diverse conditions as asthma, hypertension, thyrotoxicosis, ulcerative colitis, sinusitis and glaucoma are influenced symptomatically and perhaps etiologically by the play of the emotions.

While these significant observations have been accumulating, experience during the war has greatly emphasized the already growing recognition of the importance of emotional reactions in the development of illness. It has also brought into clearer focus the inadequacy of routine methods of examination and treatment when applied to emotional abnormalities. Actually, in the majority of the military personnel who became ill physical examination and the diagnostic application of x-rays and chemical tests failed to reveal the source of the difficulty. No specifics were available to correct faults of motivation and adjustment. To discerning physicians, the conditions of war appeared to be only an exaggeration of those in civil practice when dependence is placed chiefly on diagnostic and therapeutic procedures which cannot solve all the problems of any patient or any of the problems of many others.

Scrutiny of the rapidly accumulating experience leads to a number of generalizations of clinical significance. Physical concomitants of emotion occur in every human being. Organic disease affords no immunity and usually exaggerates anxieties and fears. Freedom from physical defects and excellent nutrition do not protect the individual from emotional disaster. Indeed, in the evaluation of disease, no diagnosis can be complete, no management optimal which does not take into account the patient's attitude and reaction to his own illness and life situation. In such observations the response of the individual can never be sharply separated into emotional and organic components. In a resentful man the effect of the situation which annoys him will be portrayed in his

nose, stomach, posture and the "sour" look on his flushed face. The entire organism reacts to an environment which it regards as threatening. Experience also indicates that while one emotional storm may lead to disagreeable symptoms, frequent repetition of the reaction over considerable periods of time is necessary before simulation of serious organic disease and physical incapacity are likely to result.

Many physicians, perhaps a majority, find themselves unprepared and relatively helpless before a patient in whom no defect can be demonstrated but who persists in being ill. In medical schools emphasis has been placed on the recognition of organic disease or of systemic conditions in which chemical abnormalities can be demonstrated. Deplorably little attention has been given to examination and evaluation of the emotional reactions of the sick man. Under these circumstances, an attitude is gaining ground both in the profession and among the laity that a patient who is ill without recognizable organic defect should seek a psychiatrist. At the same time it is recognized that there are too few psychiatrists and that more cannot be quickly trained. In the dilemma emphasis is being placed upon the necessity of immediate preparation of a group of physicians who will become interested in the interplay of physical and emotional factors and who might be called, for want of a better term, specialists in psychosomatic medicine.

There can be little question as to the desirability of training many men in this field and among them a number who will later be able to act as teachers. Separation of such a group as specialists is less defensible and may actually impede the final solution of the problem. Psychosomatic medicine is medicine itself and cannot be assigned to any one group. The analysis of a patient's reaction to life situations is as much a part of diagno-

sis as is physiology, chemistry or anatomy. Fundamental concepts which pervade understanding of all diseases must never be regarded as clinical specialties. Eventual solution of the practical problems of psychosomatic medicine must rest upon an appropriate orientation of all young physi-

cians and will depend upon broad changes in medical curricula and hospital disciplines, if it is to acquaint them from their earliest day with the physical and emotional responses of human beings under the stress of life situations.

DAVID P. BARR, M.D.

Primary Hypertrophy and Hyperplasia of the Parathyroid Glands as a Cause of Hyperparathyroidism*

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PRIMARY hyperparathyroidism is usually caused by a hyperfunctioning neoplastic tumor limited to one parathyroid gland or sometimes involving two. Occasionally, hyperparathyroidism is caused by enlargement of parathyroid tissue resulting from a remarkable primary hypertrophy and hyperplasia of water-clear cells. Albright, Bloomberg, Castleman and Churchill¹ in 1934, were the first to call attention to the clinical and surgical significance of this lesion. They described enlargement of all four parathyroid glands which was considered by them to represent hyperplasia. This enlargement was accompanied by a distinctive histologic appearance and characterized by uniformity of structure, enormous size of the cells, extreme clearness of the cytoplasm and a tendency toward glandular formation.

It is the purpose of this report to review the published cases of primary hypertrophy and hyperplasia of the parathyroid glands and to summarize the findings in four patients seen at the Mayo Clinic. Castleman and Mallory² in a comprehensive review of the pathology of hyperparathyroidism found 160 cases of hyperfunctioning lesions of the parathyroids in the literature. In twenty-five of these patients the histologic examination of the lesion disclosed only "wasserhelle" cells. In eleven patients, however, the

lesion involved only one gland; therefore, these were considered to be cases of wasserhelle adenoma or neoplasia. In the remaining fourteen patients all parathyroid tissue was involved and the condition was regarded as wasserhelle hyperplasia. In one case the lesion, classified by Castleman and Mallory (Case 112) as an adenoma, fulfills the requirements of wasserhelle hyperplasia. They added five patients seen at the Massachusetts General Hospital, which brought the total recorded instances of primary hyperplasia of the parathyroid glands up to twenty.

In our review of the literature only those cases are included in which enlargement of two or more glands was demonstrated. Four cases, which were included by Castleman and Mallory in their review (Cases 22, 92, 126 and 127), have been omitted because it was believed that the histologic descriptions given were not adequate. Since Castleman and Mallory's review appeared in 1935, two additional cases have been recorded at the Massachusetts General Hospital and eight others, including four from the Mayo Clinic, are included in this report. This brings the series to a total of twenty-six cases. Data on the twenty-two cases reported in the literature are given in Table I.

* From The Mayo Foundation and The Mayo Clinic, Rochester, Minn.

The earliest reference to wasserhelle hyperplasia is that of Möller³ in 1911. Möller mentioned the case of a woman, forty-six years of age, who died of miliary tuberculosis. Necropsy revealed two enlarged parathyroid glands measuring 4.5 by 0.5 by 0.5

case of a man, seventy-five years of age, who died of paralysis agitans and bronchopneumonia. Asymmetrical enlargement of four parathyroid glands was present at necropsy. The glands were composed of compact, medium-sized epithelial cells with

TABLE I
PRIMARY HYPERPLASIA AND HYPERTROPHY OF THE PARATHYROID GLANDS

Case	Author	Age	Sex	Surgical or Necropsy	Weight of Parathyroids	Number of Glands	Manifestations
I	Möller	46	F	N	Not recorded	2	None
II	Gjestland	75	M	N	Not recorded	4	None
III	Harbitz	75	M	N	Not recorded	4	None
IV	Bergstrand	57	F	N	400 mg., 80 mg., 145 mg. and 40 Gm.*	4	None
V	Hoffheinz	42	F	N	Not recorded	5	Nephrolithiasis; osteitis fibrosa cystica
VI	Paul	56	M	N	70 Gm.	2	Gastrointestinal; nephrocalcinosis; histologic bone change
VII	Bergstrand	55	F	N	Not recorded	4	Nephrolithiasis; weakness and polydipsia; histologic bone change
VIII	Beyerinck	35	F	S and N	Not recorded	4	Osteitis fibrosa cystica
IX	Hellström	44	F	S	Not recorded	2	Osteitis fibrosa cystica; nephrocalcinosis
X	Hanke	49	F	N	Not recorded	4	Osteitis fibrosa cystica; nephrolithiasis; nephrocalcinosis
XI	Mass. Gen.	62	F	S	10.6 Gm. (subtotal)	3	Nephrolithiasis
XII	Mass. Gen.	26	M	S	19.3 Gm. (subtotal)	4	Nephrolithiasis
XIII	Mass. Gen.	55	F	S	3.4 Gm. (subtotal)	4	Nephrolithiasis
XIV	Capps	50	M	N	35.6 Gm.	3	None; mediastinal hemorrhage
XV	Mass. Gen.	41	M	S	2.47 Gm. (subtotal)	4	Nephrolithiasis
XVI	Mass. Gen.	39	M	S	6.80 Gm. (subtotal)	4	Nephrolithiasis
XVII	Mass. Gen.	57	F	S	11.20 Gm. (subtotal)	4	Nephrolithiasis; osteitis fibrosa cystica
XVIII	Mass. Gen.	63	M	S	3.39 Gm. (subtotal)	4	Nephrolithiasis; osteitis fibrosa cystica
XIX	Hellström	60	F	S	Not recorded	2	Nephrolithiasis
XX	Hellström	59	F	S	Not recorded	2	Nephrolithiasis; nephrocalcinosis; osteitis fibrosa cystica
XXI	Thyssen	51	M	S and N	Not recorded	4	Gastrointestinal; nephrolithiasis
XXII	Flink	57	F	S	23 Gm. (subtotal)	4	Osteitis fibrosa cystica; nephrolithiasis; polyuria

* The weights recorded on Bergstrand's first case are confusing. They are recorded as 400 mg., 80 mg., 145 mg. and 40 Gm. Since Bergstrand did not comment on marked variation of size, it is presumed that the fourth weight should be 40 mg. Castleman, in writing of this case, records weights as 400 mg., 80 mg., 150 mg. and 1,040 mg.

cm. each. Histologically, they consisted of large cells with light cytoplasm. The clinical history was brief and included none of the manifestations of hyperparathyroidism. Gjestland,⁴ in 1912, recorded one

light vacuolar cytoplasm. Harbitz⁵ in 1915 and Bergstrand⁶ in 1921, each reported a case in which enlargement of all four parathyroid glands was observed. No significant clinical symptoms were mentioned in either

report. Histologically, Harbitz' patient revealed medium-sized epithelial cells with a vacuolated cytoplasm and in Bergstrand's patient the glands were composed of wasserhelle Zellen. In both patients oxyphil cells were absent. In these four patients no clinical or necropsy data were given that suggested hyperparathyroidism.

The first case of primary hypertrophy of the parathyroid glands to be associated with obvious clinical evidence of hyperparathyroidism was reported by Hoffheinz⁷ in 1925. The patient was a woman, forty-two years of age. Manifestations of bone disease had been noted for a year and for four months she had been unable to walk. Bone cysts were present roentgenologically. There were two stones in the right kidney. Death occurred from uremia. Five parathyroid glands were found and all were enlarged. Histologically, most of the cells were wasserhelle cells but a few oxyphil cells were found. Osteitis fibrosa with "brown tumors" of the bones was present.

Paul⁸ in 1931, reported the case of a man, fifty-six years of age, who had loss of appetite, weakness, fatigue and loss of approximately 28 pounds (12.7 Kg). Polydipsia was also noted. In the bones there was evidence of osteitis fibrosa. Nephrocalcinosis was observed in the kidneys. At necropsy two parathyroid glands were markedly enlarged, each weighing 35 Gm. The remaining parathyroid glands could not be identified. The histologic appearance was consistent with primary hyperplasia as the cytoplasm of the cells stained only slightly. Palisading was present.

Bergstrand⁹ again in 1931, described a case in which there was enlargement of four parathyroid glands. The patient, a woman fifty-five years of age, presented the typical symptoms of hyperparathyroidism with weakness, loss of strength, obstipation, polydipsia and polyuria. Bone pain was entirely missing. The right inferior parathyroid

gland was greatly enlarged and measured 4.5 by 2.5 by 3.0 cm. The left superior parathyroid gland likewise was enlarged and measured 4.5 by 2.5 by 0.5 cm. The remaining two parathyroid glands were enlarged, each weighing more than 100 mg. Histologically, indistinct cytoplasm with follicles was present. No Welsh (oxyphil) cells were present. In the bone there were changes of osteitis fibrosa. Bergstrand stated that histologically this patient did not present the picture of adenoma, as there was diffuse change in all of the parenchyma. He believed it was analogous to those changes seen in Basedow's struma.

In 1932, Beyerinck¹⁰ reported a case which Castleman and Mallory² subsequently classified as an adenoma of clear cells. More recent review of the microscopic sections by Snapper¹¹ showed it to be typical primary hyperplasia. The patient was a woman aged thirty-five, who complained of protracted vomiting and loss of weight. No skeletal disease was found but the concentration of calcium was 21.0 mg. per 100 cc. of serum and that of phosphorus 2.0 mg. per 100 cc. of serum. A parathyroid gland the size of a coffee bean was removed at operation. Death occurred the following day and necropsy disclosed three more abnormal parathyroids varying in size from that of a coffee bean to that of a hen's egg. Nephrolithiasis was found but the skeleton was normal on microscopic examination. Snapper stated that the sections of the parathyroid glands disclosed only large water-clear cells.

Hellström¹² in 1931, reported on a patient in whom two enlarged parathyroid glands were removed at two operations. The patient was a woman of forty-four years of age who had osteitis fibrosa cystica. The histologic appearance of the two glands was consistent with that of primary hyperplasia or the parathyroid glands. This patient came to necropsy in 1942 and the findings were re-

ported in 1944 by Hellström and Wahlgren.¹³ Two parathyroid glands of the size of a walnut were found at necropsy. Histologically, the predominant cell was the large, water-clear cell but small nodules were composed of chief cells and a few groups of oxyphil cells were observed. Cysts were identified. Hellström and Wahlgren called attention to the fact that two enlarged glands were removed at the time of operation in 1930 and the remaining two glands were of normal size. Twelve years later at necropsy, however, these remaining parathyroid glands were greatly enlarged and nodular. Nephrocalcinosis was also observed. This case is of particular interest because it is to date the only instance of primary hyperplasia with hyperparathyroidism in which there has been an opportunity for comparison of surgical and necropsy findings after an interval of twelve years.

Two additional cases in which primary hyperplasia was treated surgically were also reported in 1944 by Hellström and Wahlgren¹³ (Cases v and viii). In each patient two enlarged glands composed of water-clear cells were removed. In the first patient there was nephrolithiasis but no bone manifestations and in the second, there was osteitis fibrosa, nephrocalcinosis and nephrolithiasis. In the first instance, the serum calcium before operation was 15.4 mg. per 100 cc. and after operation it still remained high (13.5 mg. per 100 cc.).

Hanke,¹⁴ in 1932, presented the necropsy findings on a woman, forty-nine years of age, who had extremely far-advanced skeletal changes due to osteitis fibrosa cystica. The serum calcium was 23.4 mg. per 100 cc. The bone manifestations were classic. All four parathyroid glands were enlarged and histologically all cells were wasserhelle Zellen. There was nephrolithiasis and nephrocalcinosis.

Those cases described by Hoffheinz,⁷ Paul,⁸ Bergstrand,⁹ Beyerinck,¹⁰ Hellström¹²

and Hanke¹⁴ best fit the criteria of primary hypertrophy and hyperplasia of the parathyroid glands as outlined subsequently by Albright and associates.¹ It is interesting that in the reports of the earlier writers, marked emphasis was placed on the bone manifestations and lengthy descriptions of the gross and histologic appearances of the bone were given, while in many instances meager descriptions of the parathyroid glands were given.

In 1934, Albright, Bloomberg, Castleman and Churchill¹ presented data on three cases which emphasized the clinical importance of primary hypertrophy, hyperplasia and primary hyperparathyroidism* with enlargement of all parathyroid glands. They showed that surgical removal of one gland will not cure the patient of hyperparathyroidism if all four parathyroids are involved. The surgical management of these patients has been presented separately by Churchill.¹⁵

Capps,¹⁶ in 1934, reported an interesting case of mediastinal, cervical and thoracic subcutaneous hemorrhage associated with multiple parathyroid tumors. The patient was a man of fifty years of age. At necropsy the hemorrhage was found to have originated within one of the parathyroid glands. Two parathyroid glands were found grossly enlarged and a third gland was found histologically. The total weight was 35.6 Gm. Their histologic structure was identical with that reported by Albright.¹ Capps stated that neither on clinical nor on necropsy finding could the existence of hyperparathyroidism be proved or disproved.

In 1935, Castleman and Mallory² presented a classic review of the pathologic condition of the parathyroid gland in hyperparathyroidism. They reviewed the three cases from the Massachusetts General Hos-

* Hyperparathyroidism is defined as "primary" when more parathyroid hormone is produced than the body requires and as "secondary" when an increased production of parathyroid hormone is a compensatory response to some other condition.

pital originally presented by Albright, Bloomberg, Castleman and Churchill¹ and included two more of their own from the same hospital. A comprehensive review of the literature was given. They emphasized enlargement of all four glands in certain patients who demonstrated one type of cell, the wasserhelle cell. They noted that these cells had a tendency to acinar arrangement with basal orientation of the nuclei and varied from 10 to 40 microns in diameter. The nuclei of these cells, while often multiple, were approximately of the same size. The location of the nucleus at the base of the cell produced a characteristic pattern that resembled bunches of berries. The cytoplasm was clear, except for light pink staining granular material.

Castleman and Mallory¹⁷ in 1937, distinguished between the changes seen in the parathyroid glands secondary to long-standing renal insufficiency and those associated with primary hyperplasia. In the glands enlarged secondarily as a result of renal insufficiency, the gland histologically is composed of chief cells. Vacuolization of the cytoplasm may occur but the cell does not reach the size of those in patients with primary hyperplasia in whom the large water-clear cell is a constant feature.

The surgical aspects of primary hypertrophy and hyperplasia of the parathyroid glands were reviewed by Cope¹⁸ in 1935, and again by Churchill and Cope¹⁹ in 1936. Albright, Sulkowitch and Bloomberg²⁰ in 1938, presented the clinical aspects of five cases previously reported from the Massachusetts General Hospital and of a sixth case from the same hospital. The number of male and female patients was equal and the age ranged from twenty-six to sixty-two years. Renal stones were present in all six patients and bone changes were present in only one. In all patients the treatment was surgical. In one patient three enlarged glands were

identified, while in the other patients four enlarged glands were found. The amount of parathyroid tissue removed at operation ranged from 2.47 to 19.3 Gm. The remaining parathyroid tissue ranged from an estimated 0.12 to 0.5 Gm. In all patients the typical histologic picture with large water-clear cells was present. It was Albright's²⁰ opinion at this time that enlargement of the glands was the result of hypertrophy rather than of hyperplasia.

The surgical treatment of hyperparathyroidism was discussed again by Cope²¹ in 1941. He emphasized that enlargement of four glands may occur in primary hyperplasia. In 1943, Cope,²² reported the seventh case of primary hypertrophy and hyperplasia of the parathyroid glands from the Massachusetts General Hospital. Among seventy patients with hyperparathyroidism primary hypertrophy was found seven times. In the seventh instance the patient was a man, sixty-three years of age, who had renal stones and manifestations of osseous disease. All four glands were enlarged and 3.39 Gm. of parathyroid tissue was removed. The histologic appearance was identical with that previously described.²

Thyssen²³ described a case which he called adenomatous hyperplasia of all parathyroids. From his description it is another instance of typical generalized hyperplasia of clear cells. The patient, a man aged fifty-one, had typical generalized osteitis fibrosa cystica and a serum calcium value of 14.1 mg. per 100 cc. Two parathyroid glands measuring 3 by 1 cm. were removed at operation, one from each side. Anuria developed and the patient died four days following operation. At necropsy a third parathyroid gland, measuring 1.5 by 0.75 by 0.5 cm., was found on the right and a fourth gland, measuring 3 by 2 cm., was found in the superior mediastinum. On histologic examination all of the parathyroid

glands were similar in structure and were composed entirely of large, clear polygonal cells. There was no nephrolithiasis or nephrocalcinosis.

Flink²⁴ in 1945, reported the case of a woman, fifty-seven years of age, who had renal stones and bone changes. At the time of the first operation one gland weighing 3.0 Gm. was removed. As the clinical and chemical evidence of hyperparathyroidism persisted a second operation was performed. Two glands weighing 18.0 and 2.0 Gm., respectively, were removed. A fourth gland which was apparently normal in size was identified. The histologic picture of all parathyroid tissue was identical with that described in detail before. While the serum calcium dropped to normal after the second operation the bone pain persisted, the phosphorus remained low and the alkaline phosphatase and urinary excretion of calcium continued high. These findings might suggest the presence of additional hyperfunctioning parathyroid tissue.

At the Mayo Clinic four cases of primary hypertrophy and hyperplasia of the parathyroid glands have been described. During the same period sixty patients with proved hyperparathyroidism have been observed. The first case of primary hypertrophy of the parathyroids was described by Rogers²⁵ in 1946 and the second case by Rogers, Keating, Morlock and Barker.²⁶ More detailed reports of the third and fourth cases are now in the press. A brief summary of the four cases follows:

CASE REPORTS

CASE I (reported by Rogers²⁵). The patient was a man aged fifty-three. He was admitted June 4, 1945. Gastrointestinal symptoms, manifested by vomiting and epigastric pain, had been present for two years. Roentgenologic examination visualized a duodenal ulcer. Vomiting increased with institution of Sippy diet and ulcer regimen. Gastric resection was performed because of the duodenal ulcer. Vomiting reap-

peared three days after the operation. This persisted and uremia developed before death. Death occurred July 10, 1945.

At necropsy, parathyroid hyperplasia was observed. There was asymmetrical enlargement; besides the four normal parathyroid glands there were five accessory glands. The largest gland weighed 14.9 Gm. and their total weight was 20.32 Gm. Histologically, all of the cells were large, clear cells arranged in masses, cords and at times in an alveolar pattern. There was metastatic calcification of the dura mater and nephrocalcinosis. No osseous changes could be demonstrated. Because hyperparathyroidism had not been suspected during life, no data were observed on values of calcium and phosphorus in serum or urine. The necropsy findings, however, were regarded as strongly suggestive of hyperparathyroidism.

CASE II (reported by Rogers, Keating, Morlock and Barker²⁶). The patient was a man sixty-eight years old whose final admission was on October 1, 1945; he had gangrene of the left great toe. In 1919, gastro-enterostomy had been performed for a duodenal ulcer. In 1943, pain in the right foot, hip, ankles, knees and shoulders developed. In May, 1945, there was recurrence of epigastric pain, nausea and vomiting. Polydipsia and polyuria developed four months prior to last admission. Urea was elevated at the time of admission and rose from 182 to 258 mg. per 100 cc. of blood. Death occurred October 5, 1945.

At necropsy there was parathyroid hypertrophy. Six parathyroid glands were identified. The enlargement was fairly symmetrical, the two largest glands weighing 30.9 Gm. and 14.2 Gm., respectively. The total weight of the parathyroid glands was 47.56 Gm. Histologically, all of the glands were composed of large, water-clear cells. Nephrocalcinosis and multiple pancreatic calculi were present. There was osteitis fibrosa. A peculiar calcification of the intimal elastic lamina was present in many of the arteries. In this instance, as in the preceding, hyperparathyroidism was not suspected before the patient's death and clinical confirmation of its existence was not obtained. Hyperparathyroidism can be assumed with reasonable certainty from the necropsy findings.

CASE III (Case LV, reported by Black and Sprague²⁷). The patient was a woman, forty-eight years of age, who registered at the clinic May 7, 1946, complaining of pain in the right hip and both legs of two years' duration. Examination disclosed multiple renal calculi in the right kidney and generalized osteitis fibrosa cystica. The concentration of calcium in the serum was 12.4 mg. per 100 cc.; inorganic phosphorus, 0.9 mg. per 100 cc. and alkaline phosphatase, 5.7 Bodansky units. Serum proteins were 6.9 Gm. per 100 cc. and the Sulkowitch test suggested pronounced hypercalciuria.

Operation was performed May 25th by Dr. Black. On the right side a large mass weighing 50 Gm. was found. It was located behind the right lobe of the thyroid and extended from the level of the superior pole well into the superior mediastinum. It was lobulated and had many small projections on its surface. Its form gave the impression of an upper and a lower portion; since no other mass was found on the right it was assumed that this may have represented both the upper and the lower gland. On the left side two masses of similar tissue were found; an upper mass estimated to weigh about 300 mg. and a lower mass weighing 4 Gm. All, except the left upper mass, were removed and were found on examination to consist entirely of typical water-clear cells of primary hyperplasia.

The postoperative course was essentially uneventful except for mild paresthesias on the third day. The serum calcium twenty-four hours after operation was 9.3 mg. per 100 cc. and two months later it was still normal.

CASE IV (Case XIX, to be reported by Pemberton and Keating²⁸). The patient was first seen in 1940, at the age of thirty-one. He had had recurrent renal stones since 1936 and a recurrent duodenal ulcer since 1937. At the time of his first admission in 1940, right pyelolithotomy was performed for the removal of numerous calcium oxalate stones. The serum calcium at this time was 10.8 mg. per 100 cc. but a diagnosis of hyperparathyroidism was not suspected. He returned in 1943, because of recurring left renal colic. The serum calcium at this time was 11.5 mg. per 100 cc.; serum phosphorus, 2.4 mg. per 100 cc.; alkaline phosphatase, 2.8 mg. Bodansky units and serum proteins;

7.1 Gm. per 100 cc. The average daily excretion of calcium with the patient on a weighed diet was 211 mg. There was no evidence of skeletal disease.

An operation was performed July 8, 1943, by Dr. Pemberton. A soft parathyroid tumor was found behind the upper pole of the right lobe of the thyroid. It measured 2.5 by 1.0 by 0.75 cm. Because of its unusually soft consistency, Dr. Pemberton suggested the possibility that it might be hyperplastic. However, exploration did not disclose any other parathyroid tissue and the pathologic report made at the time was parathyroid adenoma.

The patient had an uneventful postoperative course. However, the abnormalities observed in the chemical composition of the blood and urine persisted unchanged and the presence of more hyperfunctioning parathyroid tissue was suspected. A low calcium, low phosphorus diet was prescribed and the patient was advised to return for periodic observation, which he did. For the next two years he remained well, despite the persistence of mild hypercalcemia. The average serum calcium was 10.5 mg. per 100 cc. and hypercalciuria was present (average daily excretion 182 mg.). The urinary tract remained normal. In the absence of further symptoms, neither the patient nor his physicians were anxious to resume the search for another parathyroid tumor, particularly when it was believed that mediastinal exploration would be required.

In February, 1946, the patient again began to have right renal colic. He returned for further examination in June and was found to have a stone 1 cm. in diameter in the pelvis of the right kidney with extensive destruction of the renal parenchyma. The serum calcium was 10.5 mg. per 100 cc.; serum phosphorus, 2.7 mg. per 100 cc. and the excretion of calcium 254 mg. per day. No evidence of bone disease was found.

A clinical diagnosis of persistent hyperparathyroidism was made and further operation was advised because of the extensive renal damage which the previous policy of temporizing had permitted. It was assumed that another parathyroid tumor would be found but because of our recent experience with Case III, the sections of the first tumor were reviewed before operation

and found to be typical of primary hyperplasia. At operation (July 3, 1946) an enlarged, left upper parathyroid was found, another enlarged gland was found at the left lower pole and a small gland was found in the right inferior position. The left superior mass was resected, leaving a tiny tag of tissue behind. The resected portion weighed 250 mg. The left inferior mass was entirely removed and found to weigh 200 mg. The small right inferior mass was also removed. Histologically, the vast majority of cells in all parathyroid tissue removed were large, clear cells but a few small nests of chief cells were identified in two of the glands.*

Postoperatively, the patient had moderate discomfort from paresthesias and exhibited positive Chvostek and Trousseau signs. No treatment was required for tetany. The serum calcium fell to 8.0 mg. per 100 cc. and the serum phosphorus rose to 4.5 mg. per 100 cc. Hypercalciuria persisted, however, the last determination before dismissal being 150 mg. per day.

ANATOMIC CONSIDERATIONS

The gross appearance of the parathyroid glands in those patients with primary hyperplasia is frequently characterized by the presence of cysts and pseudopods. This was demonstrated in those cases reported from the Massachusetts General Hospital and was likewise present in three of the four patients seen at the Mayo Clinic. The total weight of the parathyroid tissue may vary greatly, from 2 or 3 Gm. in one patient to others in which the weight exceeded 50 Gm. The greatest recorded weight of 70 Gm. occurred in Paul's⁸ case. While enlargement of all parathyroid glands is characteristic of primary hyperplasia this enlargement may be minimal in several of the glands and extreme in the remainder. In our second pa-

tient fairly symmetrical enlargement of the parathyroid glands on each side was observed; in our third, asymmetrical enlargement was present with the largest mass (which was believed to be a fusion of the right superior and the right inferior parathyroid gland) weighing 50 Gm. In this case the left inferior parathyroid gland weighed 4 Gm. and the left superior parathyroid gland was estimated to weigh 300 mg. Smaller degrees of enlargement, however, are of clinical importance, for in our fourth patient removal of two glands weighing 250 mg. and 200 mg., respectively, was sufficient to relieve persistent chemical and clinical evidences of hyperparathyroidism.

In the cases reported elsewhere, as in our own, primary hyperplasia of the parathyroid glands exhibits a basic histologic pattern. Nevertheless, our four patients show some minor variations from the basic pattern. These variations in appearance may be demonstrable in different glands from the same patient.

The most constant feature is the presence of very large clear cells,* the diameters of which range from 10 to 40 microns, which formed the major part of all glands in our patients. However, these cells may vary markedly in size so that in some regions they do not appear much larger than the water-clear cells found in small numbers in normal parathyroid tissues. In most regions the cytoplasm is water-clear but in some cells small eosinophilic granules and fine strands are present. The nucleus is for the most part constant in size and averages about 6 to 7 microns; however, some nuclei are larger

* Hellström and Wahlgren¹³ noted similar nests of chief cells in what otherwise appears to have been typical primary parathyroid hyperplasia. In Hellström and Wahlgren's patient this observation was made at necropsy twelve years after surgical resection of two glands; in both their patient and ours, nests of chief cells followed surgical resection.

* The terms *wasserhelle* and large water-clear cells have both been used interchangeably in this report to describe the histologic appearance of the cells in primary hyperplasia. Most of the older papers, especially those written in German, refer to *wasserhelle Zellen*. Inasmuch as they are probably derived from chief cells and do not represent embryologically distinct cells, there does not appear to be any value in the retention of the term *wasserhelle*. It seems preferable, therefore, to speak of these cells as large clear cells.

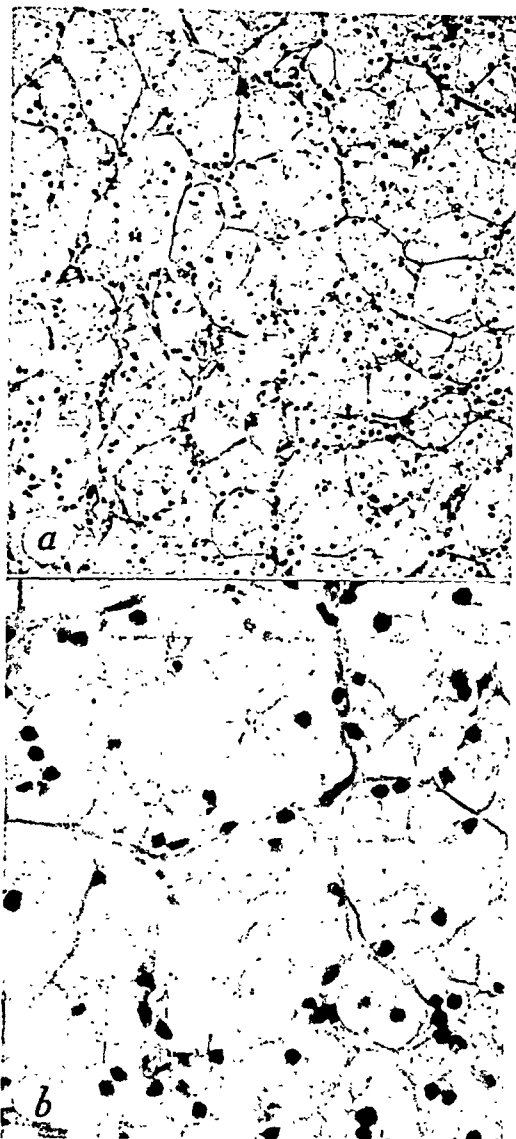


FIG. 1*a*, Primary parathyroid hyperplasia (Case III); alveolar pattern ($\times 115$); *b*, higher magnification with typical large, water-clear cells ($\times 350$).

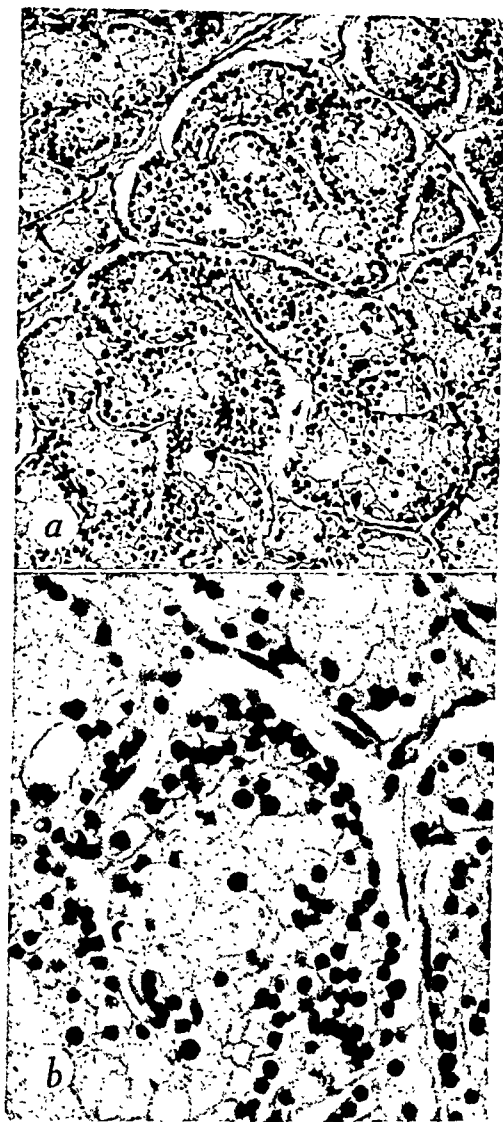


FIG. 2*a*, Primary parathyroid hyperplasia (Case II). Pseudoglandular pattern ($\times 115$); *b*, higher magnification with basally oriented nuclei ($\times 350$).

(8 to 9 microns), but none reach the size of the giant nuclei sometimes seen in adenomas. The basal orientation of the nuclei is one of the most constant features.

There is some variation in the grouping of the cells. Four distinct patterns may be found, with one gland frequently showing more than one of them. The first and most characteristic pattern is an alveolar arrangement. The water-clear cells form a lacelike pattern in which one is able to see only the

nucleus and the fine eosinophilic cell membrane. (Fig. 1 *a* and *b*.) There may be rupture of the basement membrane, producing a picture somewhat like that of pulmonary emphysema. This was first described by Castleman and Mallory.² The second pattern is characterized by grouping of cells into a pseudoglandular formation. Here, the basally oriented nuclei give a characteristic appearance. (Fig. 2 *a* and *b*.) The third pattern is a more compact arrangement of

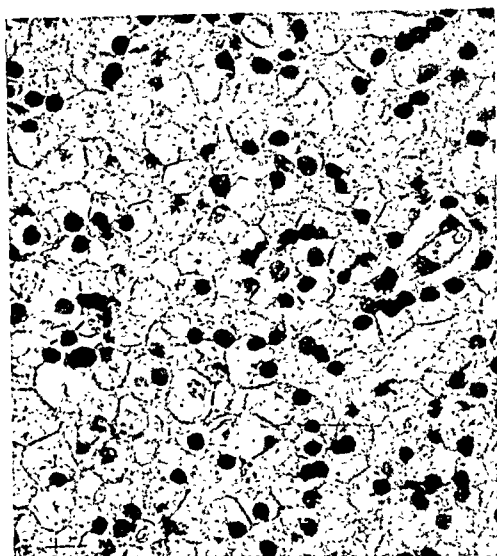


FIG. 3. Primary parathyroid hyperplasia (Case 1); compact pattern ($\times 350$).

the cells which is a relatively uncommon grouping. The cells here are smaller and there is more eosinophilic material within the cytoplasm, although the water-clear nature of the cells is readily identified. (Fig. 3.) The fourth pattern shows varying sized cysts and hemorrhage within these. (Fig. 4 *a* and *b*.) The connective tissue in most regions is sparse, appearing as delicate strands of reticulum lying between the epithelial cells and nearby capillaries. In other regions the connective tissue increases in density greatly, separating epithelial cells and capillaries. Chief cells were absent in all our patients except the fourth one (Fig. 5 *a* and *b*), where a few nests were identified.

HYPERTROPHY VERSUS HYPERPLASIA

Albright and his associates have suggested that the pathologic condition of the parathyroids under discussion is largely,²⁰ or entirely²⁹ due to hypertrophy. The chief cell of the normal parathyroid gland, according to Castleman and Mallory,¹⁷ has a mean diameter of 7 microns. Albright and his associates^{20,29} have stated that the cells in primary hyperplasia have a diameter four to five times the normal diameter. Since, as

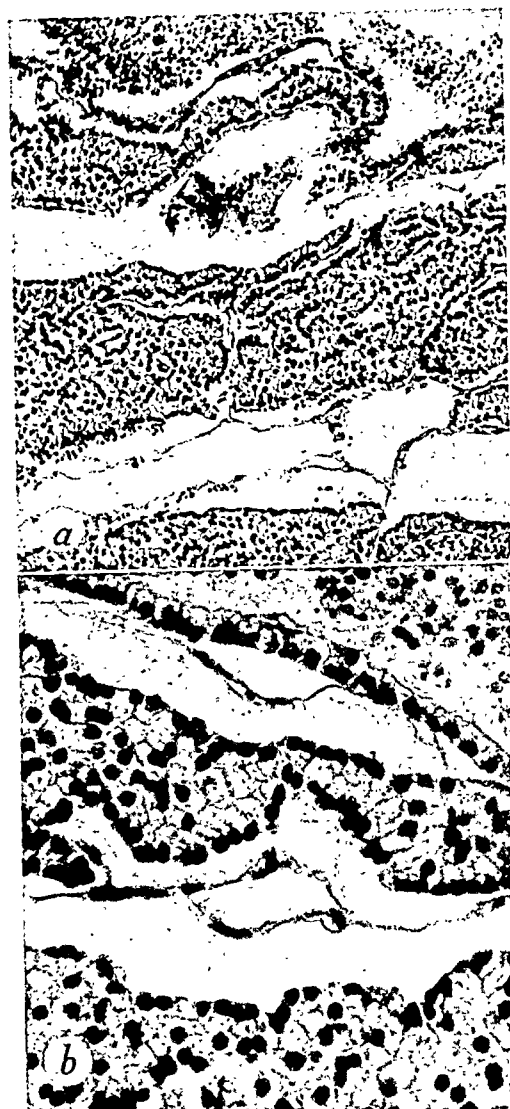


FIG. 4*a*, Primary parathyroid hyperplasia (Case II); cystic pattern; two portions of cysts in upper and lower portion, filled with erythrocytes ($\times 115$); *b*, higher magnification of upper portion reveals edge of cyst lined by cells with basally oriented nuclei. The cyst is filled with erythrocytes ($\times 350$).

they pointed out, the volume of a sphere increases as the cube of the radius, one could expect simple hypertrophy alone to account for an increase in the volume of parathyroid tissue up to sixty-four or one hundred twenty-five fold. Since the weights of the parathyroid glands in their patients varied from thirty to one hundred forty times normal, they believed that hyper-

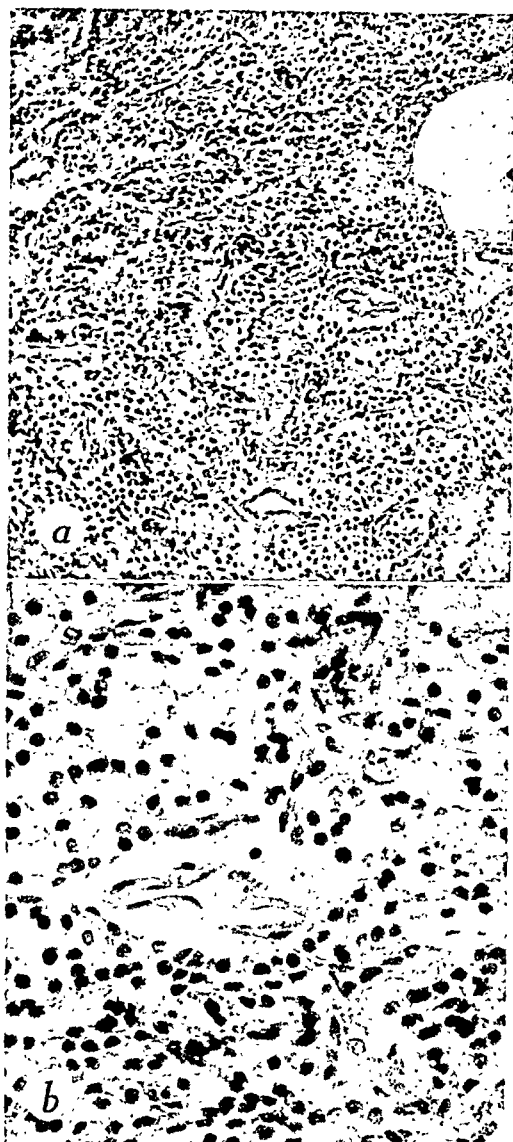


FIG. 5a, Nests of chief cells in parathyroid glands from Case iv ($\times 115$); b, higher magnification ($\times 350$).

trophy alone and not hyperplasia accounted for the enlargement.

The parathyroid tissue from the two necropsy cases which we have presented weighed 20.32 and 47.56 Gm. respectively, while that from the two surgical cases weighed 54 and approximately 3 Gm., respectively, disregarding the tissue left at operation. The mean weight of normal parathyroids is given as 117.6 mg. for men and 131.3 mg. for women.³⁰ On the basis of these figures the glands in our patients are,

in order, 170, 400, 410 and 26 times normal. After allowing for the cysts which they contain, the two largest are still too large to explain by simple hypertrophy, even if one accepts Albright's figure for a mean cell size of 40 microns. Moreover, direct measurement of mean cell size in these patients showed the mean diameter to be 21 microns, even though individual cells varied in size from 10 to 35 microns. The maximal increase in volume of parathyroid tissue which could be explained as hypertrophy alone was, therefore, twenty-seven times, which could have accounted for the weight observed in only the last patient. Further evidence in favor of hyperplasia is the fact that the total weights of the parathyroid tissue in our patients varied from 3 to 54 Gm., despite which the mean cell diameter was 20 to 21 microns in all instances. If hypertrophy alone, and not hyperplasia, was the cause of the parathyroid enlargement, one would expect a much greater mean cell diameter in those patients in whom there was the greatest mass of parathyroid tissue; this was not the case. The gross appearance of the glands was in itself suggestive of hyperplasia, particularly in the case of the larger ones. Irregularities of form and shape and the numerous projections and pseudopods were more consistent with overgrowth of cells than with simple enlargement of pre-existing cells. We, therefore, believe the condition to be one of hypertrophy and hyperplasia, with the latter playing the predominant rôle.

Pathologically at least, primary hyperplasia of the parathyroid glands appears to be analogous to the parenchymatous hypertrophy and hyperplasia of the thyroid which accompanies exophthalmic goiter and the adrenal cortical hyperplasia sometimes encountered in Cushing's disease. Whether (as in exophthalmic goiter) surgical resection will be followed by further hyperplasia and recurrence in any substan-

tial proportion of patients will be an important question for future studies to settle. Albright's experience with six patients did not disclose any tendency toward recurrence. He was impressed with the fact that the disease, once established, appeared to persist without appreciable variation and that conservative resection effected partial improvement which, while inadequate, was sustained. In Hellström's¹² first patient, however, there was almost certainly recurrence of parathyroid enlargement. At two operations in 1930 and 1931, two large, walnut-sized parathyroids were removed. A third, the size of a bean, was noted. At necropsy in 1942, two more very large glands were found which Hellström and Wahlgren¹³ stated must have enlarged in the interim. The data suggest, however, that the hyperparathyroidism persisted rather than recurred, since the postoperative values for calcium in serum remained somewhat elevated.

Our short experience with two surgical cases has thrown no further light on this matter. It is noteworthy that in our Case iv, a second operation disclosed three masses of parathyroid tissue which had not been observed at the initial exploration three years before. It might be argued that these masses had appeared as a consequence of hyperplasia after resection of the original relatively larger mass. The clinical course of the patient, however, did not favor this interpretation. Instead of the remission and recurrence which should have taken place if the foregoing explanation were valid, the patient had an unabated persistence of the original chemical abnormalities. The remarkable feature, in fact, is that no significant reduction of serum calcium or urinary calcium followed the resection of approximately 3 Gm. of parathyroid tissue, whereas the subsequent removal of an additional 450 mg. was followed by precipitate fall of serum calcium and symptoms of mild

tetany. The persistence of mild hypercalciuria, despite a normal serum calcium, is a disturbing feature which cannot thus far be explained.

On the assumption that the condition was hypertrophy alone, Albright's chief concern in the surgical management of these patients has not been recurrence, but the fear that subtotal resection sufficient to control the disease might be followed by subsequent disappearance of hypertrophy in the remnant, which would leave the patient with an inadequate quantity of parathyroid tissue and perhaps with permanent parathyroid insufficiency. There has not, to the best of our knowledge, been any evidence that this has occurred.

MORPHOLOGIC DIAGNOSIS

The gross and microscopic appearance of primary parathyroid hyperplasia must be differentiated from several entirely different pathologic entities which it somewhat resembles. These include hyperplasia of the chief cells of the parathyroid glands, metastasis of a renal cell carcinoma to the thyroid gland and adenoma of the parathyroid glands composed of large clear (wasserhelle) cells.

There may be enlargement of all four parathyroid glands in long-standing renal insufficiency. This type of secondary hyperplasia has been described by Castleman and Mallory.¹⁷ Histologically, the parathyroid glands in patients with secondary hyperplasia due to renal insufficiency are composed of chief cells alone, or in combination with oxyphil cells, in contrast to the large water-clear cells seen in those patients with primary hypertrophy. The typical appearance of chief cell hyperplasia due to long-standing renal insufficiency is shown in Figure 6 *a* and *b*. This gland was removed at necropsy from a patient sixteen years of age. Renal infection had occurred at two years of age and the terminal concentration

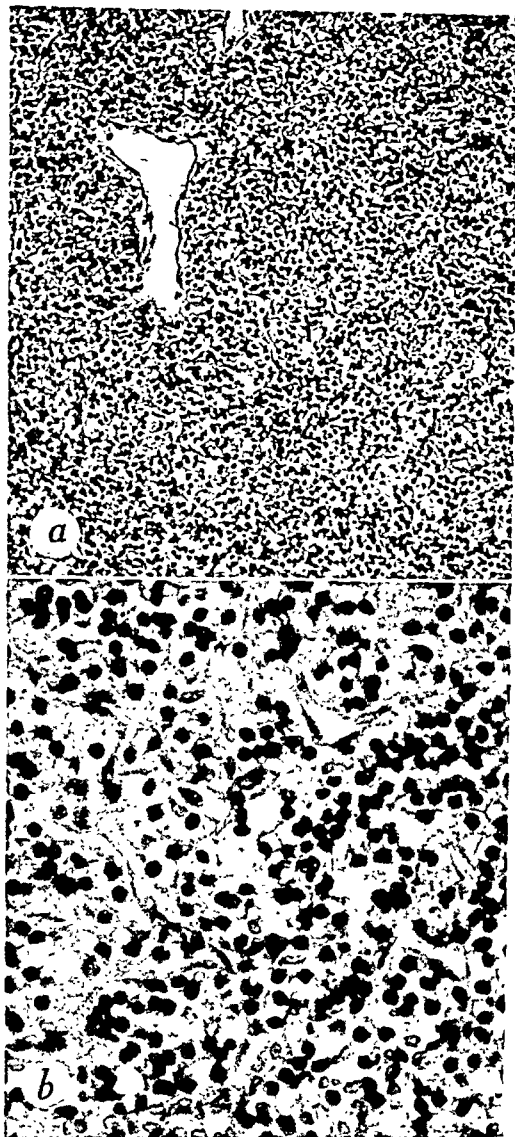


FIG. 6a, Secondary parathyroid hyperplasia due to renal insufficiency; chief cells, at times vacuolated ($\times 120$); b, higher magnification of chief cells, a few revealing vacuolated cytoplasm ($\times 350$). The small diameter of the cells is in marked contrast to the very large cells of primary hyperplasia. Compare with Figures 1b, 2b, 3 and 4b which are of the same magnification.

of urea was 600 mg. per 100 cc. of blood. The findings of healed pyelonephritis and hyperplasia of parathyroid glands were present.

Hyperplasia of chief cells indistinguishable from that accompanying renal disease is also encountered in calcium deficiency states,

including rickets (avitaminosis D), osteomalacia, sprue, pregnancy and lactation.

Renal cell carcinoma with metastasis to the thyroid may cause confusion if only histologic sections of the thyroid are examined. Castleman and Mallory² have also emphasized this and pointed out that the histologic appearance of primary hyperplasia of the parathyroid glands may resemble and actually be misdiagnosed as metastatic renal cell carcinoma. Metastasis of a renal cell carcinoma to the thyroid is not common. Long and Black³¹ in 1945, were able to find only eleven recorded instances of its occurrence. One of the most helpful differentiating features histologically is the basally oriented smaller, darker nucleus of the cells in instances of primary hyperplasia.

In the histologic diagnosis it is also to be considered that a parathyroid adenoma may consist almost entirely of large clear cells. Differentiation between an adenoma composed of large clear cells and primary hyperplasia of large clear cells depends on the demonstration of the enlargement of all parathyroid tissue in the case of the latter. The clinical course of Case iv illustrates the importance of this differentiation. Castleman and Mallory² have reported one case of their own of an adenoma consisting solely of wasserhelle cells and cited eleven possible examples occurring in the literature. It is probable that the case originally reported by Wilder, Camp, Robertson and Adams²³ is an example of this. The patient was a woman forty-eight years of age. Bone manifestations were marked and the alkaline phosphatase varied from 4 to 61.7 Bodansky units. At operation a tumor weighing 5 Gm. was removed. Histologically, it was composed almost entirely of cells with clear cytoplasm sometimes arranged in acinar formation. There was postoperative tetany followed later by severe gastrointestinal manifestations, including nausea, vomiting, cramps and diarrhea. These symptoms were

aggravated by administration of calcium and intravenous administration of sodium phosphate. Death occurred seventy-seven days after operation. At necropsy three enlarged parathyroid glands the size of a split pea were identified and histologically reported as being identical with the tumor which had been removed surgically. The bone changes were histologically consistent with osteitis fibrosa. Castleman and Mallory² reviewed this case (Case 127) in their series without having the opportunity of examining the slides and considered it an example of generalized hyperplasia of the clear-cell type. We have reviewed the histologic slides in this case. The gland removed at operation consisted entirely of large clear cells; however, in the glands removed at necropsy chief cells predominated and large clear cells were in a minority. We believe that this was an adenoma of one parathyroid gland of the wasserhelle cell type with secondary hyperplasia of the three remaining glands.* The coexistence of hyperfunctioning adenoma of one parathyroid gland with secondary hyperplasia of the remainder in the absence of renal insufficiency is most unusual. Usually the nonadenomatous glands grossly are either normal or atrophic in appearance. It is possible, therefore, that hyperplasia took place in the remaining parathyroid tissue after surgical removal of the tumor. The secondary hyperplasia in this case may have been caused by the low blood calcium maintained as a result of the extreme postoperative demands of the bones for calcium, or as a result of intravenous treatment with sodium phosphate or both. In this connection it is interesting to note that secondary parathyroid hyperplasia has been produced in rabbits by the parenteral administration of phosphate.³³

*Dr. Benjamin Castleman kindly examined the slides in this case and was in entire agreement with this diagnosis.

Throughout this report the term "primary" hyperplasia has been used to distinguish the condition from secondary hyperplasia in which the histologic appearance is different. The use of the term primary seems justified at this time because the exciting cause is unknown. It is probable that an etiologic agent or agents may be found in the future and then the term primary will no longer prove applicable. Albright and his associates¹ originally felt that the pituitary gland might well be the primary stimulating factor but in a subsequent report²⁰ they expressed the belief that the etiologic factor is unknown. In only our first patient was the pituitary gland available for study and it was histologically normal; the adrenal glands were grossly and histologically normal in the first two patients and in none of our four subjects were there clinical manifestations of disturbed function of the pituitary. In a review of the literature, Pope and Aub³⁴ concluded "that the evidence for a relation between the parathyroid glands and the anterior pituitary is neither consistent nor conclusive. If such a relation exists, it is probably not an extremely close one, for the former appear to be able to function even when the anterior pituitary is removed."

In some instances of secondary parathyroid hyperplasia, there is extensive vacuolization of the cytoplasm of the chief cells, which like the hyperplastic process *per se* may represent a cellular response to the stimulus which induces hyperfunction (elevated serum phosphorus, lowered serum calcium or both?). In these instances the vacuolated cells resemble in size and nuclear characteristics the normal chief cell but their clear cytoplasm resembles that of the much larger water-clear cell of primary hyperplasia. Perhaps the remarkable cellular changes in patients with primary hyperplasia represent merely an extensive degree of the same type of response to stimulation;

in this case to a stimulus of unknown character and origin.

The case reported by Lober, Hertzog and Rice³⁵ is an example of vacuolization of chief cells in secondary parathyroid hyperplasia due to renal insufficiency. Their patient had hyperparathyroidism with osteitis fibrosa cystica. A parathyroid adenoma composed of chief cells was removed. Death from renal insufficiency occurred three years later. Nephrocalcinosis with tubular obstruction was marked. The parathyroid glands removed at necropsy were described as consisting almost entirely of wasserhelle cells, although the evidence in this case pointed to renal insufficiency as a cause for the enlargement. Measurements of cell diameters were not given and the magnification of the photomicrographs was not stated. Through the kindness of Dr. A. J. Hertzog we have had the opportunity of reviewing the slides. The mean diameter of the cells in the parathyroid glands removed at necropsy was found to be 10 to 12 microns, with the largest cells not exceeding 15 to 16 microns. Their size is considerably smaller than that of the large water-clear cell typical of primary hyperplasia. We agree with Lober, Hertzog and Rice that the glands examined at necropsy represent secondary hyperplasia due to renal insufficiency and believe the clearness of the cytoplasm represents vacuolization of chief cells as described by Castleman and Mallory. We do not believe that they should be termed wasserhelle cells or confused with primary hyperplasia as they are much smaller.

CLINICAL CONSIDERATIONS

In the majority of the reported cases of primary hyperplasia the patients have had obvious hyperparathyroidism. Bergstrand⁹ was the first to suggest that primary parathyroid hyperplasia is the counterpart in the parathyroids of exophthalmic goiter in the thyroid. At the present time this concept

appears to be justified. We believe that the histologic picture of primary hyperplasia always indicates a primary excess of parathyroid hormone. However, it must be pointed out that in five (Cases i, ii, iii, iv, and xiv in Table 1) of the twenty-two cases reported elsewhere neither clinical nor pathologic evidences of hyperparathyroidism were described. The first four of these reports appeared before 1925, when hyperparathyroidism was first described as a clinical entity and the fifth patient died before careful clinical appraisal could be concluded. As all five were necropsy cases the absence of any notation regarding bone lesions or nephrolithiasis may be significant but such omissions do not exclude entirely the possibility that some degree of previous hyperparathyroidism might have been present in these instances also. In the first two cases reported from the clinic, hyperparathyroidism was not suspected or confirmed during life but the necropsy findings made a diagnosis of hyperparathyroidism highly probable.

It is important to consider whether the hyperparathyroidism resulting from primary hyperplasia differs either qualitatively or quantitatively from that resulting from neoplastic lesions of the parathyroids. Keating and Cook,³⁶ on reviewing twenty-four cases of primary hyperparathyroidism (twenty-three of which were due to parathyroid tumor) which were seen at the Mayo Clinic during a period of two and one-half years, found that in a third of them there was classical osteitis fibrosa cystica; in another third, there was minimal bone disease, and in a third there was no clinical evidence of bone disease whatever. In twenty-two of the twenty-four cases there was some degree of renal involvement. These observations agree closely with those of Albright and his associates but are in marked contrast to the majority of cases of hyperparathyroidism reported from other sources.

In most published cases of hyperparathyroidism there has been severe and usually extreme osteitis fibrosa cystica; despite Albright's contributions, most other observers have not recognized the disease in the absence of severe skeletal disease. We believe, as Albright does, that this is so because the disease is not intensively sought, as it should be, among patients presenting themselves because of nephrolithiasis or nephrocalcinosis.

In twenty-one of the twenty-six cases of primary hyperplasia there have been findings which warrant a diagnosis of hyperparathyroidism; in nine of these classic osteitis fibrosa cystica has been present, in three there have been milder degrees of skeletal involvement evident only on histologic examination and in nine there has been no evidence of skeletal disease. In sixteen there has been nephrolithiasis, in four there has been nephrocalcinosis and in one there has been no evidence of renal disease. So far as present experience indicates, therefore, there appears to be no reason to consider that the hyperparathyroidism of primary hyperplasia is qualitatively any different in its manifestations from that resulting from tumor. By the same token there are no clinical means by which a patient shown to have the clinical and chemical manifestations of hyperparathyroidism can be predicted to have hyperplasia instead of neoplasia; the surgeon must be prepared to encounter either lesion in every patient in whom exploration is performed for hyperparathyroidism.

Analysis of the data available does not justify a definite conclusion that, in the aggregate, hyperplasia produces a less intense form of hyperparathyroidism than tumor but there are several reasons for inferring that this may be the case. In the first place, in only two of the earlier cases of osteitis fibrosa cystica due to hyperplasia did the bone disease reach the extreme, deforming proportions described in many of

the cases due to parathyroid tumor. In the second place, it is noteworthy that in the impressive series of patients with hyperparathyroidism observed at the Massachusetts General Hospital, where careful study has led to the recognition of the disease in milder forms which presumably might have been overlooked elsewhere, parathyroid hyperplasia has been encountered surgically seven times and accounts for approximately 10 per cent of the patients having hyperparathyroidism; in five of the seven patients there was no skeletal involvement. At the Mayo Clinic prior to 1943, hyperparathyroidism was diagnosed fourteen times in fourteen years; in all but one of the patients there was relatively severe bone disease and all were due to tumor. Since 1943, as a result of careful search for the disease, particularly in patients who had renal stones, hyperparathyroidism has been encountered in forty-three surgical and three necropsy cases, the skeletal manifestations of which have been, at least on the average, very much milder than those in earlier series. In two of the forty-three surgical and two of the three necropsy cases the lesion has been primary hyperplasia. Our recent experience, therefore, has been comparable with that of Albright.

By contrast, only ten of all of the cases of hyperparathyroidism reported from other sources have proved to be due to hyperplasia and only six of these, Beyerinck's,¹⁰ the three of Hellström¹² and those of Thysen²³ and Flink,²⁴ have been surgical cases. When the milder and less extreme forms of hyperparathyroidism are sought, hyperplasia would appear to account for 5 to 10 per cent of the patients but in the literature as a whole it accounts for an insignificant fraction.

In the two necropsy cases of primary hyperplasia which we have reported, the chief manifestations which were afterward attributed to hyperparathyroidism were gas-

gastrointestinal. The possibility that these manifestations may complicate the treatment of hyperparathyroidism or may confuse the diagnosis, as well as their importance, has been emphasized earlier.^{25,26} The occurrence of gastrointestinal manifestations probably attributable to hyperparathyroidism in two of four patients who had hyperplasia might appear significant. However, of the twenty-two cases of hyperplasia observed elsewhere, in only those of Paul⁸ and Beyerinck¹⁰ is the patient mentioned as having major gastrointestinal symptoms. It is curious to note, however, that in three of our four cases of hyperplasia there were or had been active duodenal ulcers. We have noted the coexistence of duodenal ulcers in approximately one third of all the patients with hyperparathyroidism who have been seen at the clinic. This association seems too frequent to be coincidence but one can only conjecture as to its meaning.

SUMMARY

Primary hyperplasia of the parathyroid glands is a distinct pathologic entity. Twenty-two cases have been collected from the literature; the morphologic and clinical aspects of these and four additional cases seen at the Mayo Clinic have been discussed. Primary hyperplasia must be differentiated from parathyroid adenoma composed of clear cells, from metastatic renal cell carcinoma to the thyroid and from secondary parathyroid hyperplasia. The question of hypertrophy versus hyperplasia has been discussed; evidence is given for assuming that both are present but that the latter predominates. The clinical implications of primary hyperplasia are discussed. In twenty-one of twenty-six patients primary hyperplasia was accompanied by primary hyperparathyroidism; it is probable that the condition always represents primary parathyroid hyperfunction.

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The Shoulder-Hand Syndrome*

Associated Painful Homolateral Disability of the Shoulder and Hand with Swelling and Atrophy of the Hand

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THIS report is based on six patients, among over 200 cases of painful dysfunction of the shoulder, presenting the peculiar combination of painful shoulder disability with homolateral swelling of the hand. In five patients the swelling of the hand was followed by trophic changes. In almost every instance the condition had been diagnosed at some time or other as rheumatoid arthritis, usually of the atypical variety. Some of the patients had been treated with gold salts, radiation therapy and a variety of measures employed in rheumatoid disease. Other diagnoses were scleroderma, bursitis and periarthritides, infectious arthritis and scalenus anticus syndrome. Whether the clinical picture about to be described is merely symptomatic of a complicated form of fibrositis in the shoulder and neck region, some vascular or neurological disturbance, particularly a sympathetic neuropathy, remains unestablished. Nevertheless, owing to the distinctive diagnostic and prognostic features of this disorder it merits special emphasis, perhaps even classification as a separate entity.

As far as can be discerned from our small series, the condition goes through three stages of evolution: The first consists of a painful disability of the shoulder with generalized swelling and stiffness of the hand and fingers appearing with acute painful onset or developing insidiously over

three to six months. (Fig. 1.) Either the shoulder or hand symptoms may arise first, followed by involvement of the other part, or both may be affected simultaneously and gradually. The next phase, during another three to six months, consists of gradual relief of pain and dysfunction noticeable at the shoulder, accompanied as a rule by resolution of the swelling of the hand. Stiffness and flexion deformity of the fingers, however, become more pronounced as the swelling is absorbed. (Fig. 3.) Osteoporosis is increasingly distinguishable in films of the hand and shoulder. (Fig. 2.) The third stage of the picture then follows as trophic changes in the hand become noticeable. Limited flexion and stiffness of the fingers remain troublesome. Contracture of flexor tendons, especially on the ulnar side, occurred in four of the patients. This disabling and disfiguring feature has lasted five years in one patient and is still present in another after seven years. (Fig. 4.) The symptoms and signs follow a rather typical pattern in their development, character and resolution, varying merely as to severity and duration in individual cases. In the mildest the whole clinical picture from onset to recovery took ten months; the most severe case after 7 years still exhibits partial, and possibly irreversible, disability of the shoulder and hand with contractures of three fingers.

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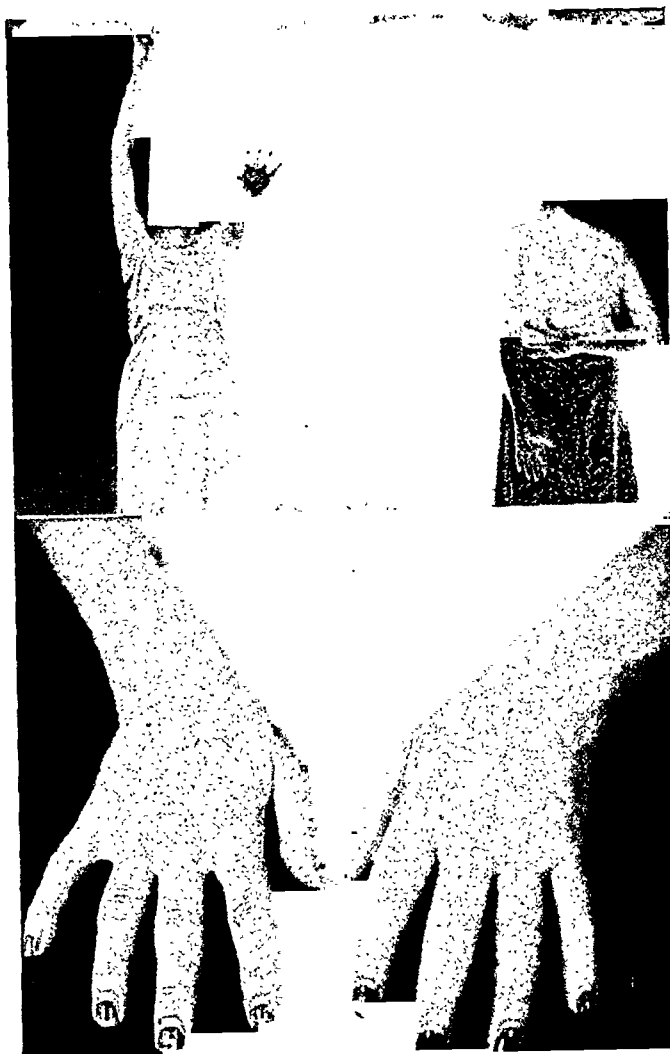


FIG. 1. (Mrs. I. B.) First stage of shoulder-hand syndrome: Diffuse swelling from wrist down over dorsum of hand and throughout the digits of three months' duration; associated shoulder pain and disability of six months' duration.

Shoulder discomfort and limited motion in all directions resemble the symptoms in periarthrititis. Diffuse tenderness about the joint is elicited during the period of involvement. Swelling of the shoulder area was seen in only one of the cases. The swelling of the hand develops below the wrist, is uniform and generalized over the metacarpals and digits with little or no pitting. The hand may appear pinker than the opposite one and increased heat of the part may be demonstrated. Sometimes the swol-

len tissues are pale or cyanotic. Stiffness of the articulations persists throughout the clinical course. Widespread tenderness to palpation is found but is no greater about the joints. When atrophy occurs, it seems to be due to a more or less uniform shrinkage of subcutaneous tissue and muscle in the hand and fingers. Contractures appear to be tendinous. An antecedent history of infection or trauma was obtained in only one of the patients, who gave a story of a mild "sprain of the shoulder" before his

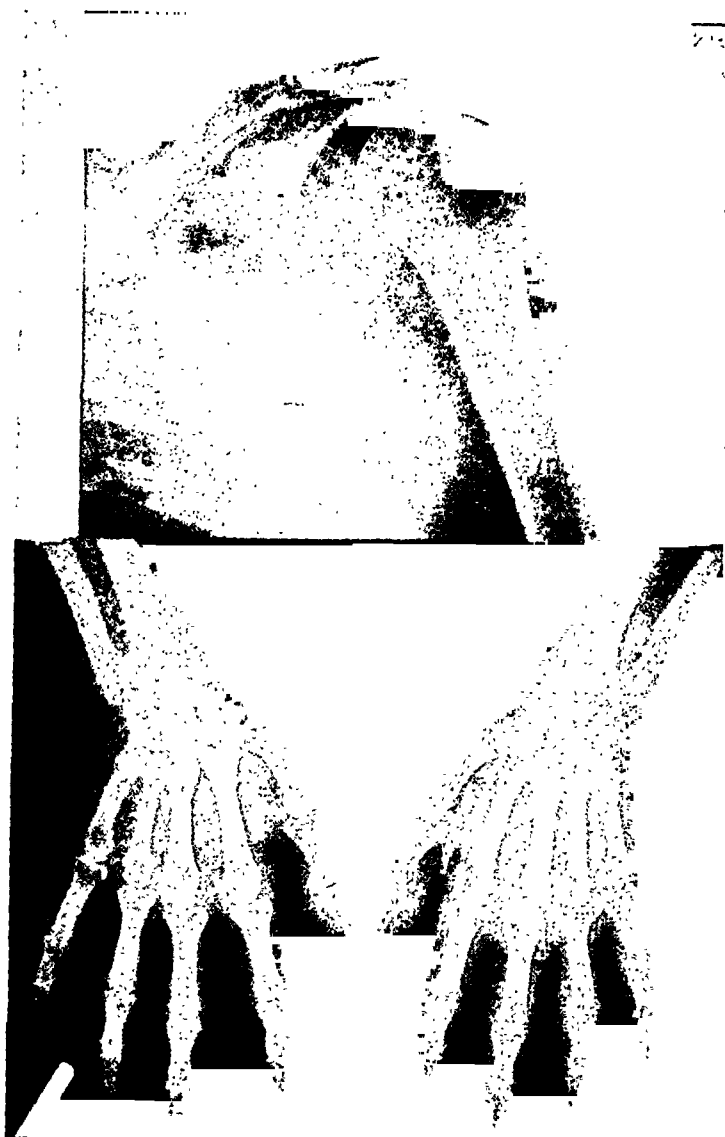


FIG. 2. X-ray films of hands and affected shoulder of patient in Figure 1 showing decalcification of wrist and hand and some osteoporosis at humeral head.

symptoms appeared. Five of the patients were under great emotional strain. Two showed moderate to severe osteoarthritis of the cervical spine. (Table 1.)

Differential diagnosis requires exclusion of a number of similar conditions according to the stage of the disorder; most frequently atypical rheumatoid arthritis and, in the later phases, scalenus anticus syndrome and scleroderma. The only resemblance to the scalenus syndrome lies in the tenderness of the scalenus area, along with other points

of soreness in the neck and shoulder and weakness of the grip. Injection of the scalenus anticus muscle with procaine proved ineffective. The possibility that the swelling of the hand represents compression of an anomalous subclavian vein running beneath the muscle, instead of over it, was not confirmed in one patient subjected to exploration.

The appearance of the hand in the shoulder-hand syndrome is only suggestive of rheumatoid arthritis. The swelling of the hand and digits is uniform, affecting all of

them diffusely, instead of being limited to the periarticular area of one or several joints as in rheumatoid disease. The tenderness to palpation also is generalized and is elicited equally anywhere on the hand. The persistent homolateral involvement of the shoulder and hand without symptoms in other joints or even on the other side of the body is unlike the behavior of rheumatoid arthritis. When seen during the most florid stage the sedimentation rate was elevated in one of the six cases.

A condition similar to this shoulder-hand disorder in almost every other detail, but usually affecting both hands in addition to one or both shoulders, has been described by Askey¹ and exhaustively by Johnson,² who termed the disorder post-infarction sclerodactylia. These authors, among others, have reported its appearance three to sixteen weeks after myocardial infarction, or in association with symptoms of angina pectoris. Unfortunately, the electrocardiograms of two of our patients seen eight and nine years ago are not available. All patients in our series, however, were free from any clinical signs of cardiac disease and gave no history of angina or infarction. Among the post-infarction patients reported in the literature, males predominated, while five of our six subjects were females. The thirty-nine patients of Johnson showed bilateral hand involvement. Some of the trophic terminal changes described and illustrated in post-infarction sclerodactylia were unlike those seen in our cases.

The patients in this series developed no cardiac symptoms even during the course of extensive follow-up. The possibility of a preceding infarction cannot be excluded because the patients were not seen and electrocardiographic and clinical study was not carried out until what would have been a long period after the initial coronary occlusion. It is conceivable but unlikely that six consecutive patients would be seen with



FIG. 3. (Mrs. J. S.) Intermediate stage of the disorder of eight months' duration; swelling of hand almost gone, flexion posture of fingers definite, trophic changes becoming noticeable; shoulder disability still present. Flexion deformity of digits has lasted five years; shoulder function recovered about three months after this photograph was taken.

silent infarctions without a history of some symptoms or of anginal complaints. Even from the meager information supplied by so few cases, one cannot help suspect under the circumstances that the shoulder-hand disorder may develop also in patients free from coronary disease. Its position in this respect may well be analogous to painful disability or periarthritides of the shoulder, as well as Dupuytren's contracture. Each of these has been reported in a relatively high percentage of patients with angina pectoris or myocardial infarction. Yet they occur frequently in otherwise healthy individuals.



FIG. 4. (Mrs. M. B.) Terminal stage with contractures of fingers and residual shoulder disability seven years after onset; observed throughout typical stages of clinical picture.

In our cases of the shoulder-hand syndrome recovery occurred spontaneously by slow stages. The shoulder discomfort and disability subsided within three to twelve months. The swelling of the hand resolved within a similar period. The trophic changes of the hand were more slowly replaced by normal appearance and function after approximately two years and four years in two patients. After seven years the changes still persist in another. One patient has been under observation for less than a year and has developed atrophy in the last two months. In the mildest case there was only

muscle weakness which seems to have improved without any residual atrophy. One patient did not remain under observation after the initial study.

Acute bone atrophy, causalgia, post-traumatic osteoporosis, reflex dystrophy or Sudek's atrophy is suggested by this clinical picture.³⁻⁶ The signs and osteoporosis were similar in many ways in our cases but they developed much more insidiously than in Sudek's atrophy. The trauma or suppuration usually preceding the syndrome described by Sudek was lacking completely in five of our 6 patients. It is possible that

TABLE I

Patient	Age	Sex	Occupation	Side Affected	History of Trauma	Cardiac or Coronary History	ECG	E.S.R.	Changes Cervical Spine (Films)	Result	Duration of Hand Disability
A. J.	55	F	Housewife	R	0	0	Normal	Normal	Moderate	Recovery	2 yr.
J. S.	45	F	Housewife	L	0	0	No record	Normal	0	Recovery	5 yr.
M. B.	58	F	Housewife	R	0	0	Normal	52 m.m.	Moderate	Contracted 3, 4, 5 digits still present; slight residual at shoulder	7 yr.
M. R.	52	F	Housewife	R	0	0	No record	Normal	0	Unknown	Unknown 10 mo.
J. P.	52	M	Metal plater	R	"Sprain" of shoulder	0	Normal	Normal	0	Recovery; slight weakness hand muscles	
I. B.	49	F	Housewife	L	0	0	0	Normal	0	Recovery; slight weakness hand muscles	18 mo.

some minor trauma or torsion may have occurred without our patients' noticing it, as surgeons have postulated in similar clinical pictures. It is just as likely that such an assumption merely leads us away from other causes ultimately to be established.

A group of fourteen patients presenting swelling and atrophy of the hand, in many respects like our cases, has been reported by Oppenheimer.⁸ Apparently his patients did not present the associated shoulder disability. In all of the cases the upper cervical spine showed intraforaminal constriction by bony spurs to which the author attributed the clinical picture. Cervical osteoarthritic changes were found in only two of our patients. It is possible the special radiographic technic employed by him would increase the number showing these peculiarities. The clinical course described differs in many ways from that of our patients.

From this small series it appears that the shoulder-hand syndrome observed in the majority of our cases resembles in some features "post-infarction sclerodactylia," Sudek's atrophy, and the swollen atrophic hand with cervical osteoarthritis described by Oppenheimer. Yet it differs sufficiently to suggest a distinctive syndrome. These disorders probably have a common relationship in the neurovascular reflex mechanism which seems to underlie all of them. They may, therefore, represent variations of sympathetic and spinal reflex reactions to different etiologic factors: trauma, myocardial infarction, intraforaminal constriction by bony spurs and the "idiopathic" group, as in our patients, in which the cause remains to be established.

Treatment of the shoulder-hand syndrome has not been extensive enough so far to permit of definite conclusions. Diathermy to the cervical spine and deep

x-ray therapy have been recommended by others.^{8,9} In post-traumatic and other reflex dystrophies favorable results have been reported from paravertebral sympathetic nerve block and, in unresponsive cases, sympathetic nerve section.⁴⁻⁷

SUMMARY

In the six patients described here the shoulder-hand syndrome proved to be a painful, disabling condition leading in some instances to long standing, and in one case possibly permanent, trophic changes of the hand. Its appearance requires thorough study of the patient and evaluation of the cardiac status. For the present it must be regarded in cases like ours as a non-traumatic, non-cardiac, idiopathic disorder acting through a disturbed neurovascular mechanism. If the differentiation of this clinical picture serves only to avoid unsuitable therapy and to provide a better insight into the prognosis, its recognition as a special entity is justified.

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The Altered Response of Human Beings to the Intramuscular Administration of Typhoid Vaccine during Massive Salicylate Therapy*

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THE parenteral administration of typhoid vaccine to normal subjects usually results in the development of circulating antibodies to this organism. In addition, this toxic bacterial protein causes a transient rise in the plasma fibrinogen, the erythrocyte sedimentation rate and total leukocyte count as well as a transient decrease in total lymphocytes. Often there are local reactions at the sites of injection. Systemic reactions also may occur. A rise in serum "gamma globulin" as determined chemically follows administration of the vaccine. In order to determine what modifying influences might result during salicylate medication, we have studied the effects of the injection of typhoid vaccine in a control group of eighteen adults as contrasted with fourteen patients receiving massive doses of salicylates. In all instances measurements of the formation of antibody to the typhoid organisms were performed. In several subjects in the group, additional studies included the frequent determinations of total serum protein, serum albumin, serum globulin, plasma fibrinogen, "gamma globulin," volume of packed red cells, erythrocyte sedimentation rate and total leukocyte and differential leukocyte count. From these measurements, it was hoped to gain further information as to the mode of action of salicylates.

MATERIAL AND METHODS

The control group of eighteen adults, eleven males and seven females, consisted of thirteen healthy hospital personnel, two patients with multiple sclerosis, one patient with arteriosclerotic heart disease and two patients with active rheumatic fever. Their ages ranged from twenty-one to forty-eight years. Nine of this group gave a history of previous injections of typhoid vaccine within five years prior to the present study while the other nine subjects denied having received typhoid vaccine or having had typhoid fever.

In the group of fourteen individuals who were receiving massive salicylate therapy at the time of administration of the vaccine, there were nine females and five males whose ages ranged from nineteen to forty-one years. Eight of these patients had acute rheumatic fever; three, rheumatoid arthritis; two, dermatomyositis; and one was thought to have periarteritis nodosa. Nine of these patients had been immunized previously within the past five years with typhoid vaccine. In the entire group of fourteen subjects, salicylate medication had been administered for 7 to 132 days before the injections of typhoid vaccine for the present study. The plasma salicylate levels in the week preceding and for two weeks after administration of the antigen were main-

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tained between 300 and 410 micrograms per cc. of plasma in twelve of the fourteen patients and between 200 and 300 in the other two patients. Salicylate therapy was discontinued at intervals varying from sixteen to seventy days after immunization, the average duration of salicylate medication being thirty-five days after the injections of vaccine.

The vaccine employed was stated to contain one billion typhoid and 500 million paratyphoid A and paratyphoid B organisms per cc. The protein content of the washed bacterial suspensions varied from 80 to 110 micrograms of nitrogen per cc. Each subject received 1 cc. of this vaccine intramuscularly in the deltoid area. A second injection of 1 cc. was administered forty-eight hours later in the same area. Each injection was made in the evening.

The typhoid antibodies were measured with twofold dilutions of serum in saline, beginning with a dilution of 1:20 so that, after adding an equal volume of organisms the final volume of the initial dilution was 1:40. The typhoid H antigen was prepared by treating a suspension of bacteria with 0.2 per cent formalin while the O antigen was prepared by treatment of live organisms with ethyl alcohol. The original typhoid H antigen showed a definite agglutination in stock rabbit antiserum which was diluted to 1:5,120 but no visible agglutination in the next dilution. The original O antigen showed definite agglutination in a 1:640 dilution of the antiserum but not in antiserum diluted to 1:1,280. Each subsequent lot of antigen was tested with this same stock rabbit antiserum. No new antigens were employed which differed from the original antigens by more than one dilution in their sensitivity to agglutination in the stock rabbit antiserum.

The serial dilutions of the sera to be examined plus the H or O antigen were placed in a water bath for five hours

at 56°C. The H antibodies were read immediately after incubation while the O antibodies were read after subsequent refrigeration at 4°C. for eighteen hours. In a few instances, the same sample of human serum was checked after storage to determine the relative constancy of the antibody titer with different lots of antigens. The antibody titers for H antigen did not vary more than one dilution. The H antibodies are detected readily. The O antibodies, however, are more difficult to read and less accuracy was possible in their measurement. Following the administration of vaccine, antibody titers for sera were determined twice during the first week, thrice during the second week and, thereafter, once a week for many weeks. For convenience the antibody titers are expressed as the reciprocals of the saline dilutions of the sera. Arbitrarily we have considered sera with less antibody than 1:40 as containing no antibodies.

In nearly all instances blood specimens for protein studies and for determination of erythrocyte sedimentation rate, leukocyte count and differential leukocyte count were drawn between 10 and 11 A.M. At least two samples of blood were examined in the two weeks interval prior to the administration of the vaccine. For this study, blood was withdrawn daily from the subjects for six days following injection of the vaccine, three times during the second week, twice during the third week and thereafter weekly for periods of three to twelve weeks. Since the typhoid vaccine was administered in the evening, the initial blood specimens were obtained about 18 hours later. All glassware was chemically clean. Salicylate levels of the plasma were determined thrice weekly by the method of Brodie and coworkers.¹ All protein measurements were made with the biuret method of Kingsley.² Lipemic sera were treated with ethyl ether before making a colorimeter reading. The plasma

fibrinogen was determined by the method of Cullen and Van Slyke³ by measuring the protein content of the clot of oxalated plasma. This was prepared by adding 1 cc. of plasma to 28 cc. of normal saline and 1 cc. of 0.1 M calcium chloride. The serum

phoretically this fraction of Cohn contains 3 per cent alpha globulin, 70 per cent beta globulin and 25 per cent gamma globulin).⁸ Moreover, the "gamma globulin" fraction as determined chemically with ammonium sulfate is found to be greatly increased in

TABLE I
STATISTICAL EVALUATION OF VARIOUS PROCEDURES AS CARRIED OUT IN NORMAL PERSONS

Blood Constituent	No. Persons	No. Determinations	Median	Range of 90% of Values	Total Range	Standard Deviation Due to Method	Possible Error of Method in Per Cent
Total Protein Gm. per cent.	29	218	6.94	6.20-7.59	5.60-7.99	±0.033 Gm.	±0.48%
Albumin Gm. per cent.	21	166	4.43	4.00-4.89	3.50-5.49	±0.029 Gm.	±0.65%
Total Globulin Gm. per cent.	22	161	2.59	1.80-2.99	1.20-3.59		
Albumin: Total Globulin.	22	162	1.85	1.40-2.39	1.20-3.59		
"Gamma" Globulin Mg. per cent.	32	168	788	550-1049	500-1149	±0.021 Gm.	±2.66%
"Gamma" Glob.: Total Prot.	33	165	11.4	8.5-13.9	7.0-14.9		
Fibrinogen Mg. per cent.	17	143	262	200-329	170-349	±0.009 Gm.	±3.44%
Sedimentation Rate Mm. per hour.	13	118	6.4	0-14.9	0-21.9		
Hematocrit Reading Cc. per cent.	15	179	46.5	42.0-52.9	38.0-54.9		
White Blood Count cells per c. mm.	13	126	6882	5000-9999	4000-11999		
Lymphocytes cells per c. mm.	8	54	2480	1600-3999	1200-4399		

Standard deviation due to method calculated from triplicate determinations of serum from ten normal individuals.

albumin and total globulin determinations were made with 23 per cent sodium sulfate, using the Howe method.⁴ The initial two-fifths of the filtrate was discarded as recommended by Gutman and coworkers.⁵ The "gamma globulin" fraction was obtained by adding saturated ammonium sulfate to undiluted serum to a saturation of 33 per cent. This was accomplished under controlled pH determinations (measured with glass electrode) and with care as to the rapidity of precipitation. This method has been described briefly elsewhere⁶ and will be described in detail later.⁷ It is sufficient to state here that the 33 per cent ammonium sulfate precipitate of human sera contains certain antibodies present in Fraction II of Cohn (electrophoretically Cohn's Fraction II contains 98 per cent gamma globulin) while it contains no significant amount of other antibodies (typhoid O and isoagglutinins) present in Cohn's Fraction III-1 (electro-

certain diseases in which elevated gamma globulin values have been observed by electrophoretic studies. The sedimentation rate of whole blood and the volume of packed red cells were determined by the method of Wintrobe.⁹ The sedimentation rates were not corrected for the presence of anemia for this was not present to any great extent in any subject used in this study. The total leukocyte counts were determined by counting four large squares of a standard counting chamber. Differential leukocyte counts were performed by random selection of 100 leukocytes on blood smears drawn on glass cover slips and stained by Wright's method.

In Table I are given normal values for these procedures in our hands, using the methods mentioned above. A large number of determinations have been made on a relatively small number of controls. This was done to determine the constancy of the

various constituents from day to day in a given individual.

The addition *in vitro* of sodium salicylate in concentrations of 1,000 micrograms per cc. (expressed as salicylic acid) to whole serum or plasma and incubation for eighteen hours at 37°C. using sterile technic, failed to demonstrate that this amount of salicylate modified in any way the determination of antibody titer, plasma fibrinogen, total serum protein, albumin, globulin, or the serum "gamma globulin" content as compared with serum or plasma incubated without salicylate.

RESULTS

Both the control subjects and the patients receiving sodium salicylate were subdivided into those who gave a history of having had previous typhoid vaccine and those who never had received this vaccine. In the latter group, failure to recollect vaccine administration previously, and the possibility of asymptomatic or unrecognized typhoid infection previously, could not be excluded.

In the control subjects the initial intramuscular injection of typhoid vaccine usually was attended by a moderately severe local inflammatory reaction characterized by redness, heat and local discomfort. With the second injection forty-eight hours later, the local reactions invariably were less severe than after the initial injection. No distinct difference in intensity of local reaction could be detected in the nine control subjects who had not been immunized previously (Group I) as compared with the nine who had been immunized previously (Group II). In one of nine members of Group I and in seven of nine subjects in Group II, there occurred systemic reactions following the first or second injection. These consisted of headache, malaise, anorexia and fever usually lasting only twenty-four hours. In three of the ten subjects with

systemic reactions the temperature exceeded 103°F. Systemic reactions were more frequent after the second injection than after the first. When systemic reactions followed the first injection, they became intensified after the second injection.

By contrast, local reactions in the patients receiving salicylate medication were mild and short lived. Only three of these fourteen patients developed significant erythema and heat at the site of injection. No systemic reaction followed administration of the vaccine in any of the fourteen patients who were receiving salicylates. This included nine patients who had been immunized previously.

The antibody response to the H antigen of the typhoid organism in the control subjects and in the patients receiving sodium salicylate showed considerable individual variation as regards time of appearance of antibodies, maximal antibody titers and duration of circulating antibodies. In the control subjects the initial rise in antibody titer usually appeared about the fifth day after injection of vaccine, reaching a maximal titer at the end of one week, gradually falling thereafter. As illustrated in Figure 1 and in Table II, the H antibody titer (mean values) rose much higher in those control subjects who had been immunized previously with typhoid vaccine (Group II) than in those who had not (Group I). Two subjects without previous immunization failed to develop any H antibodies with this program of immunization. In the nine controls who previously had been given typhoid vaccine, three had residual antibody titers of 40 to 160 at the time this experiment was begun. In no member of this previously immunized group was an immediate increase of antibody to the H antigen observed in the specimen taken eighteen hours after the initial injection. All nine subjects in the group with a history of previous immunization developed significantly elevated titers

of antibodies to H antigen following vaccination. (Table II.)

Antibody titers to H antigen in the patients receiving large doses of salicylates were much lower. (Fig. 1, Table II.) In those patients receiving salicylates who gave

typhoid vaccine. In the entire group of nine patients (Group IV) the rise in antibody titer to H antigen was much less than that observed in the group of nine control subjects (Group II) who had been immunized previously. Since the differences in the mean

TABLE II
NUMBER OF INSTANCES IN WHICH VARIOUS ANTIBODY TITERS WERE OBSERVED IN
CONTROL SUBJECTS AND IN PATIENTS RECEIVING SALICYLATES

Group	No. Subjects	Antibody Titer to Typhi H								No Anti-bodies	Titer before Injection		
		40	80	160	320	640	1280	2560	5120		40	80	160
I	9	7	7	7	5	4	2	0	0	2	0	0	0
II	9	9	9	9	9	9	5	3	1	0	3	2	1
III	5	1	1	0	0	0	0	0	0	4	0	0	0
IV	9	8	8	4	2	2	0	0	0	1	3	2	1

Group	No. Subjects	Antibody Titer to Typhi O								No Anti-bodies	Titer before Injection		
		40	80	160	320	640	1280	2560	5120		40	80	160
I	7	5	4	3	2	1	1	0	0	2	0	0	0
II	8	8	7	4	3	3	0	0	0	0	2	0	0
III	3	2	1	1	0	0	0	0	0	1	0	0	0
IV	5	5	4	3	0	0	0	0	0	0	2	0	0

Group I = Control subjects not previously immunized.

Group II = Control subjects previously immunized.

Group III = Patients receiving salicylates not previously immunized.

Group IV = Patients receiving salicylates previously immunized.

no history of previous antigen administration (Group III) none had antibodies prior to injection of the typhoid vaccine. Four of the five failed to develop any circulating antibody (less than forty) to the H antigen although two of these did develop low antibody titers to the O antigen. In the nine patients receiving salicylate medication who gave a history of previous vaccine administration (Group IV), three had antibody titers of 40 to 160 prior to the new injections of this substance. This appears significant inasmuch as these three patients had been receiving large doses of salicylates for at least four weeks before their injections of

titers of antibody content in these two groups exceeded two dilutions, this finding appears significant. As we have indicated earlier, the expected error in the method does not exceed one dilution.

Greater individual variation in antibody response to the O antigen than the H antigen was observed in all groups. Frequently this antibody appeared several days earlier than the H antibody and usually disappeared more rapidly. In those controls who had been immunized previously, an apparent anamnestic response was encountered in three of the eight subjects in whom determinations of O antibody titer were made 18

hours after the initial injection of vaccine. This consisted of a rise in the antibody titer to values of 40 to 160. While the number of observations is small, the results as indicated in Table 2 suggest that some depression of O antibody formation occurred in the patients receiving salicylate medication as opposed to the controls.

During the course of salicylate therapy additional typhoid vaccine (1 cc. intramuscularly) was administered to three patients (Group III, two patients; Group IV, 1 patient) in whom the antibody response to the two injections of vaccine three to six weeks previously had been poor. In the two patients from Group III, a rise in antibodies to H antigen occurred after this new injection. However, the maximal titer following the new injection still was less than that observed in the control group to whom only two injections had been given. In the subject from Group IV, the rise in antibody titer following the new injection was slight and transient in character.

Three patients in Group III and two patients in Group IV received an additional 1 cc. of typhoid vaccine intramuscularly one to four weeks after discontinuation of salicylate medication and two to ten weeks after the two previous injections had been given. In all five a rise in antibody titer occurred after the new injection and in four this reached a maximal titer which was above that encountered following the two injections which were given during the course of salicylate therapy. In one patient, however, the rise in antibody titer to H antigen was very slight with this new injection. Previously this patient had developed no antibodies to the H antigen.

A few additional immunologic studies have been made. In three patients in whom initially there was a high antifibrinolysin content in the serum during active rheumatic fever, no apparent reduction in titer occurred during a prolonged course of

salicylate therapy during which high plasma salicylate levels were maintained. The antifibrinolysin content of serum was performed by a slight modification of the method of Tillett.¹⁰ In two patients in whom Dick and Schick tests were negative prior to

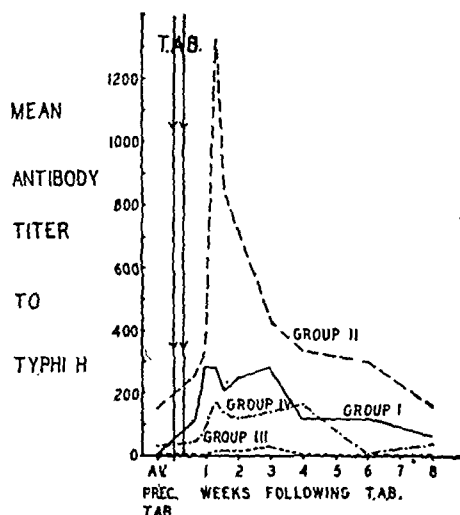


FIG. 1. Group I comprises nine control subjects without a history of previous administration of vaccine. Group II consists of nine control subjects who had been immunized previously with typhoid vaccine. Group III consists of five patients, not previously immunized, who were receiving large doses of salicylates while Group IV is composed of nine patients receiving salicylate medication in whom previous immunization had been carried out. Note the striking difference in antibody titer in Group II as compared with Group IV. "Av. Prec. T.A.B." refers to the average titer of two determinations made prior to injection of vaccine. "T.A.B." refers to the vaccine which consists of typhoid, paratyphoid A and paratyphoid B organisms.

salicylate therapy, repetition of these tests during the third or fourth week of salicylate medication still resulted in negative tests.

In a small group of controls and of patients receiving salicylate medication, we have determined the total leukocyte count and the absolute numbers of lymphocytes per c. mm. daily for six days after injection and two to three times per week thereafter

for two subsequent weeks. Since no apparent differences in the behavior of the total leukocyte and lymphocyte counts were observed between those subjects who had been previously immunized and those who had not, we have not separated these groups.

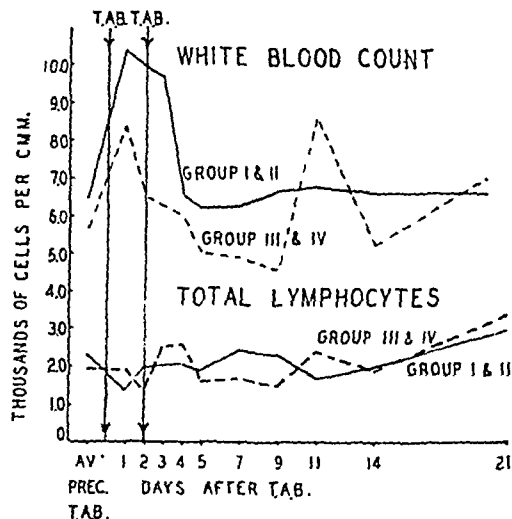


FIG. 2. The mean values for total leukocyte count and total number of lymphocytes per c.mm. in control subjects (Groups I and II) and in patients receiving salicylate medication (Groups III and IV) after administration of typhoid vaccine. Note the apparent greater leukocyte response in the control subjects as opposed to those receiving salicylate following injection of vaccine. It is uncertain whether the difference in the degree of reduction in numbers of lymphocytes in these two series is significant. (For explanation of groups, see Figure 1.)

Total leukocyte counts were followed in eight controls and in four patients receiving salicylate medication following typhoid vaccine. As is indicated in Figure 2, there occurred a moderate rise in the leukocyte count eighteen hours after the initial injection with no further rise following the second injection. The leukocyte count returned to its original level by the fourth day. By way of contrast, the leukocyte rise in the four patients receiving salicylate medication was smaller.

In six controls and in four patients receiving salicylates, the administration of

typhoid vaccine was followed by a decrease in the absolute numbers of lymphocytes per c. mm. following the initial injection of typhoid vaccine. The reduction in lymphocytes was maximal at eighteen hours after the initial injection in the control group and eighteen hours after the second injection in the patients receiving salicylates. The rise in the total leukocyte count at a time when the lymphocyte count was decreasing was attributable to an increased number of granulocytes.

In nine control subjects and in seven patients receiving salicylate medication, we have made simultaneous determinations of the plasma fibrinogen and the erythrocyte sedimentation rate following administration of typhoid vaccine. No differences were noted in the subjects who had been immunized previously as opposed to those who were immunized for the first time. In the control group the rise in plasma fibrinogen was maximal thirty-six hours after the first injection and showed no further rise following the second injection. The fibrinogen returned to normal ranges within five days after the initial injection. No rise in plasma fibrinogen occurred in the patients receiving salicylates following administration of the typhoid organisms. (Fig. 3.)

The erythrocyte sedimentation rate in the control group showed a maximal rise on the third day after the initial injection and fell to the initial level over a period of eleven days. (Fig. 3.) It is apparent that the erythrocyte sedimentation rate lagged behind the plasma fibrinogen in the time required to attain the peak value as well as in the time taken to return to normal.

As is illustrated in Figure 3, the mean value for plasma fibrinogen prior to injection was slightly higher in the patients receiving salicylate medication whereas the mean erythrocyte sedimentation rate was considerably higher in those patients receiving salicylate medication than in the

controls. Actually the mean value in the patients receiving salicylate medication distorts the truth inasmuch as five of the nine patients receiving salicylate medication had initial erythrocyte sedimentation rate and plasma fibrinogen values as low as the initial

sistent changes were observed in the total serum protein, serum albumin or total serum globulin after the typhoid vaccine. The serum "gamma globulin," however, did increase following the first injection of typhoid vaccine in the control subjects. It re-

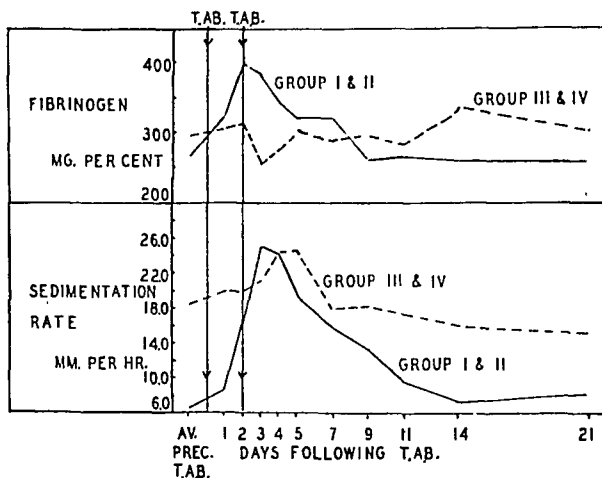


FIG. 3. Mean values for plasma fibrinogen and erythrocyte sedimentation rate in nine control subjects of Groups I and II, and in seven patients receiving salicylate medication in Groups III and IV, following administration of typhoid vaccine. Note the greater increase in plasma fibrinogen and in erythrocyte sedimentation rate in the control subjects.

values of the control subjects. In these five patients with normal values as in the four others in whom moderate elevation of fibrinogen and erythrocyte sedimentation rate occurred, there was no increase after administration of the vaccine.

In the control group, a slight delayed decrease in the volume of packed red cells occurred after administration of vaccine. In the group receiving salicylates the hematocrit readings were not constantly depressed and showed no distinct trend.

The total protein, albumin, globulin and "gamma globulin" of the serum were determined at frequent intervals after injections of typhoid vaccine in ten control subjects (five of Group I; five of Group II) and in eight patients receiving salicylates (three of Group III and five of Group IV). No con-

turned to normal within seventy-two hours after the first injection. A secondary rise in this fraction was noted again from seven to nine days after the initial administration of typhoid vaccine. (Fig. 4.) In the patients receiving salicylate medication, no immediate or delayed rise in the "gamma globulin" occurred.

In Figure 5 we have depicted the variations in the various components as determined in ten healthy adults. In this group, blood specimens were taken once each week and the mean values for each week are indicated in the chart. It is apparent that the mean variations observed in this control group were much less than the changes occurring in the control subjects who received typhoid vaccine. In addition, we now have followed these various protein constituents

at weekly intervals in twenty normal individuals for three months and have observed no variation comparable to that observed in the control subjects receiving typhoid vaccine. The same finding obtained for five control subjects in whom these determinations were made daily for six days.

by suitable parenteral routes in relatively large doses.

It seems reasonable to ascribe to the toxic action of the bacterial proteins, the inflammatory reaction observed at the site of injection. Why there is a less marked local reaction to a second injection of equal size

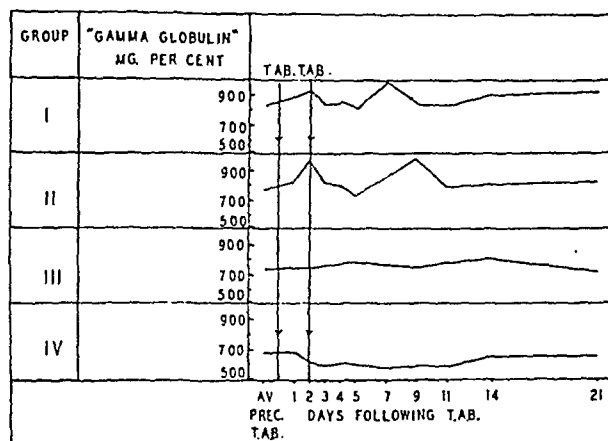


FIG. 4. Mean values for serum "gamma globulin" in ten control subjects from Groups I and II and in eight patients receiving salicylates in Groups III and IV after injections of vaccine. Note the immediate (second day) and delayed (sixth to tenth day) rises in "gamma globulin" in the control subjects after vaccination as opposed to the relatively slight change occurring in the patients receiving salicylate medication. (For explanation of groups, see Figure 1.)

COMMENTS

Before discussing the changes observed in the patients who received salicylates, it is important to consider the possible factors involved in the production of the changes that were observed after injection of typhoid organisms in the control subjects. The vaccine employed, which is a mixture of antigenic proteins, leads to the formation of specific antibodies. In addition, the vaccine contains bacterial proteins which may give rise to symptoms of sensitization in subjects who have received this substance previously. Finally, the bacterial proteins are toxic agents which, apart from any process of immunization or sensitization, produce local and systemic reactions when administered

forty-eight hours later is not clear. In part the systemic reaction may be due to absorption of toxic proteins although, as we have indicated, systemic reactions usually occurred only in those individuals who had received this vaccine at an earlier date. In individuals in whom typhoid vaccine is administered intravenously, febrile reactions and systemic symptoms occur regularly. A rise in the plasma fibrinogen and in the erythrocyte sedimentation rate which we observed in the control subjects after the injections of the typhoid organisms also has been reported by Ham.¹¹ The increase in plasma fibrinogen is probably the most important factor in the production of an elevated erythrocyte sedimentation rate.^{11,12,13,14}

However, as is illustrated in Figure 3, the increase in plasma fibrinogen alone does not explain entirely the observed elevation of the erythrocyte sedimentation rate in our cases since the elevation persisted after the plasma fibrinogen returned to normal. Contributing to the production of an elevated

group of nine patients who have no history of immunization with the other nine controls who had been immunized previously. Strikingly different was the incidence of systemic manifestations; these were observed in only one of nine of the previously non-immunized controls but were observed in seven of nine

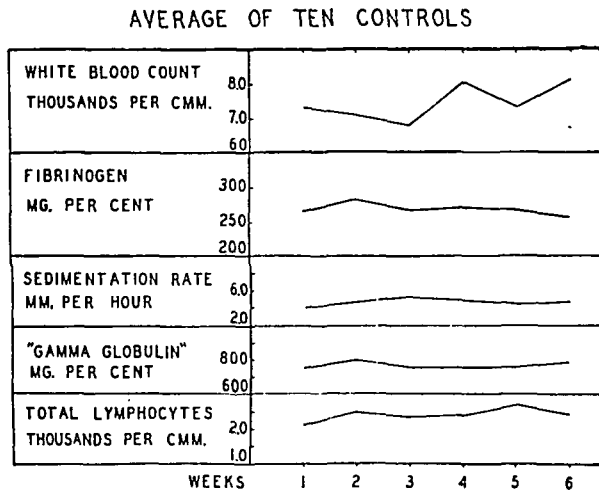


FIG. 5. Mean values for plasma fibrinogen, erythrocyte sedimentation rate, serum "gamma globulin," total leukocyte count and total lymphocyte count per c.mm. in ten control subjects. Each constituent was determined once weekly in each subject for six weeks. Note the relative constancy of these mean determinations from week to week.

erythrocyte sedimentation rate, apart from anemia, are increases in the globulin or lipid content of the plasma^{11,12} and possibly other changes in plasma constituents.

Favorite and Morgan,¹⁵ who injected a purified somatic antigen of the typhoid bacillus intravenously into man and rabbits, observed a rapid rise in the total leukocyte count and in the numbers of granulocytes following the injection. It appears likely that the similar response which we observed after injection of typhoid vaccine intramuscularly, resulted from the toxic action of bacterial proteins.

The possible rôle of bacterial sensitization such as might have resulted from previous injections of the typhoid vaccine, can be considered only by contrasting the control

who had been immunized previously. The only other significant variation between these two control groups was the higher antibody titer in the sera of the previously immunized subjects after readministration of the vaccine.

Before considering the changes observed in the "gamma globulin," lymphocyte counts and antibody titers of the control subjects, it is useful to recall current concepts about the interrelation of these components. Evidence indicates that antibodies are formed in the lymphocytes of lymphoid tissues.^{16,17,18} Antibodies present in blood are largely contained in the gamma globulin fraction although some are included in the beta globulin fraction as determined electrophoretically.⁸ It has been demonstrated that normal lympho-

cytes contain gamma globulin.^{19,20} White and Dougherty¹⁹ reported that extracts of lymphoid cells from immunized animals contained a striking increase in gamma globulin. These investigators also have shown that adrenal cortical steroids when administered to animals, result in rapid depletion of lymphocytes in lymphoid tissue and in decreased numbers of circulating lymphocytes.²¹ This is accompanied by a prompt increase in the total protein and gamma globulin fraction of serum.¹⁹ The stimulus for increased release of adrenal cortical steroids is initiated by adrenotrophic hormone which, when administered parenterally, produces changes comparable to those observed after injections of adrenal cortical steroids.¹⁹ Moreover, various toxic chemical reagents and even injection of sheep cells into rabbits may give rise to pituitary-adrenal cortical stimulation as evidenced by a lymphopenia following injections of these substances.²² The cumulated evidence thus indicates that the lymphocytes are an important source for gamma globulin synthesis (including antibodies) and release of this protein fraction from the lymphoid tissue into the circulation is controlled in part, at least, by pituitary-adrenal cortical stimulation. After a single injection of either adrenal cortical steroids or adrenotrophic hormone, the lymphopenia, depletion of lymphoid tissue, increase in gamma globulin and in total serum protein is transient, the maximal effect occurring before twelve hours and largely disappearing after twenty-four hours. With repeated injections, these changes tend to persist.

Presumably a similar mechanism accounts for the lymphopenia that has been observed to occur in man in the period of three to twenty-four hours after intravenous administration of various bacterial proteins.²³

Dole, Watson and Rothbard²⁴ observed that in beta hemolytic streptococcal infections,

there was a general correlation between the increase in gamma globulins as measured electrophoretically with the titer of anti-streptolysin although the increase in anti-streptolysin titer *per se* would not seem to be sufficient to account for the marked elevation of the serum gamma globulin that was observed frequently in these patients.

There is no conclusive evidence at the present time that all serum gamma globulin is derived from lymphocytes. Moreover, it is possible that protein depletion or other factors still unknown may impair antibody production without implying any defect in the lymphocyte mechanism in instances where antibody production is impaired.^{19,25,26}

As has been indicated, a decrease in total lymphocytes and a rise in "gamma globulin" was observed in the control subjects following administration of typhoid vaccine. This effect was greatest at the end of eighteen hours and rapidly disappeared thereafter. It is possible that even greater changes in these constituents might have occurred if similar studies had been made earlier than eighteen hours after injection of the vaccine. Without any significant change in the total lymphocytes per c. mm. a second rise in "gamma globulin" was observed on the ninth day and largely disappeared by the eleventh day after administration of vaccine. (Fig. 4.) This secondary increase in "gamma globulin" coincides with the time of development of maximal circulating antibody titer to the typhi H antigen. This does not imply that the rise in "gamma globulin" on the ninth day was attributable wholly to an increase in antibodies to the typhi vaccine. This is even more apparent when it is noted that while the "gamma globulin" returns to normal rapidly, the decrease in circulating antibodies to the typhi H antigen is slow, the high titers often persisting for many weeks.

In the patients receiving massive doses of salicylates the observed changes occurring after administration of typhoid vaccine differed strikingly from those noted in the controls. Local reactions were milder in the patients receiving salicylates. No systemic reaction occurred in any patient receiving salicylate medication after administration of the vaccine. This appears significant inasmuch as seven of nine control subjects who had been immunized previously developed systemic reactions after readministration of vaccine while none of nine subjects receiving salicylates in whom immunization had been instituted previously developed any systemic reaction. There was no significant rise in the plasma fibrinogen, the total leukocyte count or the total number of granulocytes in the patients receiving salicylate medication. Likewise, no significant increase in plasma fibrinogen or erythrocyte sedimentation rate, and no immediate or delayed rise in "gamma globulin" occurred in this group. It did appear that some reduction in total lymphocytes per c. mm. followed the injection of the vaccine in the patients receiving salicylate medication. Antibody production appeared to be impaired significantly in the patients receiving salicylates as opposed to the controls.

Swift injected various antigens into rabbits receiving large doses of salicylates and observed that circulating antibody production was impaired but not blocked completely in these animals.²⁷ Homburger²⁸ observed marked reduction of circulating antibody titer after administration of large doses of salicylates to rabbits and guinea pigs that were receiving injections of rhesus cells. In man, however, the evidence that salicylate medication impairs antibody production is equivocal. Perry²⁹ found no impairment of antibody response following administration of typhoid vaccine to patients who were receiving 2 to 3 Gm. of acetylsalicylic acid daily. Coburn and

Moore³⁰ administered salicylate therapy prophylactically to groups of rheumatic subjects at a time when they developed beta hemolytic streptococcal pharyngitis. The dosage was 4 to 6 Gm. a day. The anti-streptolysin response in the group receiving salicylates was similar to that in a control group. Rantz, Boisvert and Spink³¹ treated a group of patients with hemolytic streptococcal pharyngitis with 10 Gm. of sodium salicylate daily for one week. This did not diminish the percentage of individuals exhibiting an antibody response and did not reduce the mean increase in antistreptolysin. With the exception of the latter study, the doses of salicylates employed may be considered as inadequate to produce significant plasma salicylate levels. In no instance was mention made of determinations of the plasma salicylate level. Our own studies appear to indicate that typhoid vaccine administered to patients in whom high plasma salicylate levels (300 to 400 micrograms per cc.) are maintained, evokes less circulating antibody production than occurs in control subjects. We did observe that circulating antibodies to the typhoid H antigen may persist during prolonged courses of salicylate medication in patients who have residual antibodies from previous typhoid vaccine administration. Here, however, renewed administration of antigen did not result in as great an increase in antibody titer as might be expected from the response of the antibody titer in previously immunized control subjects to whom this vaccine was readministered. The argument that the patients receiving salicylate medication might not be able to develop high antibody titers because of their disease (rheumatic fever, rheumatoid arthritis, etc.) does not seem valid inasmuch as two subjects with acute rheumatic fever not treated with salicylate developed antibody titers as high as healthy control subjects after injection of typhoid antigen.

It is difficult to ascribe the differences in response to typhoid vaccine between the control group and the group receiving salicylate medication to any single mechanism. A number of possibilities present themselves.

The apparent failure to observe the changes in the salicylate group as opposed to the control group might be explained by assuming that the salicylate medication in some way modified the bacterial proteins so as to render them less toxic and less antigenic. Swift²⁷ reported that incubation of typhoid organisms with salicylates prior to administration into rabbits receiving salicylate medication resulted in less antibody formation than was observed in rabbits which were immunized with untreated antigen while receiving salicylates. He does not define clearly the concentration of salicylate which was employed in treating the typhoid organism but his statements suggest that it was a far higher concentration than could be obtained *in vivo*.

A further possibility is that the injected organisms and their toxins are removed more rapidly from the circulation than in the controls. Beeson³² observed that after repeated administration of typhoid organisms to rabbits, their febrile response became less with succeeding injections and was restored to its former magnitude when the reticulo-endothelial system was blocked by injections of thorotrast. This seemed to indicate that the reticulo-endothelial system removed the organisms more rapidly from the circulation in these hyperimmunized animals. At present we have no information as to whether or not salicylate medication stimulates the reticulo-endothelial system.

The failure to observe a rise in serum "gamma globulin" and the impaired antibody response in the patients receiving salicylate medication suggests impaired production of antibody by the lymphocytes either directly or indirectly through the

pituitary-adrenal cortical stimulation. As additional evidence it may be pointed out that we have observed in both normal subjects and in patients with acute rheumatic fever or rheumatoid arthritis that prolonged administration of large doses of salicylates with maintenance of plasma salicylate levels above 300 micrograms per cc., produces a definite decrease in the serum "gamma globulin" as determined chemically.³³ This finding should be confirmed with electrophoretic studies in order to preclude certain difficulties which might arise from qualitative changes in the proteins in patients receiving salicylate medication.

Finally, there is a certain amount of evidence which indicates that salicylate medication results in selective liver damage. It is conceivable that with impaired liver function, the necessary precursors for antibody production may be lacking. The most striking evidence of impaired liver function in patients receiving salicylates is the hypoprothrombinemia which may occur. Elsewhere we have considered this problem and have presented other evidence for selective liver damage in patients receiving salicylate medication.^{34,35} Recently, Rapoport and Guest³⁶ reported that the decrease in plasma fibrinogen which frequently is observed in patients receiving salicylate medication is additional evidence of selective liver damage since this decrease in plasma fibrinogen also was noted in patients with diseases other than rheumatic fever while massive doses of salicylates were being administered. Our finding that the plasma fibrinogen does not rise after administration of typhoid vaccine would be in accord with this view. However, it is equally possible in our cases that the milder local reactions observed to occur in patients receiving salicylate medication after injection of typhoid vaccine might have afforded less stimulus for an increase in plasma fibrinogen.

CONCLUSIONS

Typhoid vaccine was administered intramuscularly to eighteen control subjects and to fourteen patients who were receiving massive salicylate therapy.

Antibody formation to the typhoid H and O antigens was suppressed in the patients receiving salicylate medication as opposed to the control subjects.

Individuals receiving typhoid vaccine intramuscularly usually develop a transient leukocytosis with an increase in granulocytes and a lymphopenia. In addition, a rise in the plasma fibrinogen and in the erythrocyte sedimentation rate occurs after injection of vaccine. As determined chemically, the "gamma globulin" fraction of serum increases immediately following vaccine administration, returns rapidly to its original level and then rises again during the second week following vaccine administration. This secondary rise coincides with the development of the maximum antibody titer to the typhi H antigen.

In patients receiving salicylate medication, these changes do not occur or are slight in character following injection of vaccine.

In patients previously immunized with typhoid vaccine, readministration frequently results in systemic reactions. No systemic reactions occurred, however, in previously immunized patients receiving salicylate medication when the vaccine was reinjected.

Possible means whereby salicylate medication alters the response to typhoid vaccine are considered.

Dr. M. M. Wintrobe and Dr. George Sayers gave aid in the criticism of this manuscript.

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Gastroscopy with Transparent Balloon^{*}

Method for the Visualization of the "Blind Areas"

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WITH the flexible gastroscope (Wolf-Schindler) about four-fifths of the stomach can be visualized. There are, however, a number of important areas that cannot be seen. These are the so-called "blind areas"^{1,2} or "zones interdites."³ The extent of these areas varies somewhat with the shape of the stomach and the conditions under which the examination is performed. Figure 1 is a schematic drawing of the stomach in the left lateral position with the usual blind areas labelled alphabetically. A description of the drawing follows:

A represents the lesser curvature of the antrum. This area is often difficult to visualize because of the angulation of the stomach. The examination of the antrum is important since a great number of malignant lesions are situated in that region; B represents a small part of the greater curvature forming the lower pole of the stomach and a strip of the posterior wall on which the gastroscope lies. This zone is often the site of the stoma of posterior gastroenterostomy where marginal ulcers may arise;⁴ C illustrates a region high up in the fundus which is hidden from view. Unfortunately, this is an area which is also difficult to examine roentgenologically because manual compression of this portion is unsatisfactory; D represents a small zone on the posterior wall near the cardia and 1 to 2 cm. of the lesser curvature immediately below the cardia where the objective is too close to the mucosa. The mucosa may be lifted somewhat by the device suggested by Rogers.⁵ This method may

also be used for the examination of the posterior wall and greater curvature. (Fig. 1, zone B.)

Of these four zones the "blind area" of the antrum is the most important as radiologists are often unable to make a definite

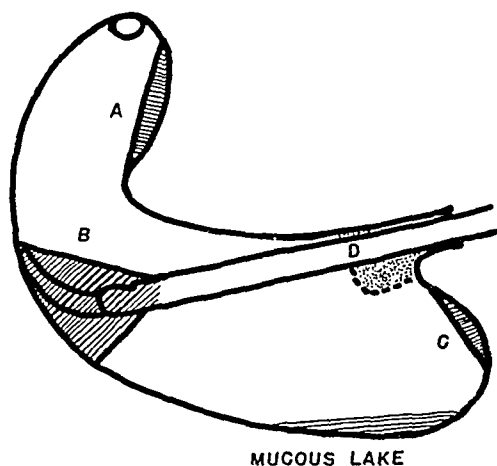


FIG. 1. "Blind areas" of the stomach. The shaded areas, A, B, C and D, are seldom visualized during gastrosopic examination.

diagnosis of the nature of craters seen in this region. Gastrosopic examination of this area during various phases of respiration with observation of the peristaltic movements may enable one to study the antrum to greater advantage.^{1,2,6,7} In the majority of instances, however, it is still impossible to visualize the lesser curvature satisfactorily. Berry⁸ suggests that gastrosopy be performed with the patient in the right lateral position, since he observed in twenty-four examinations that "the visualization of the blind area of the antrum was improved in

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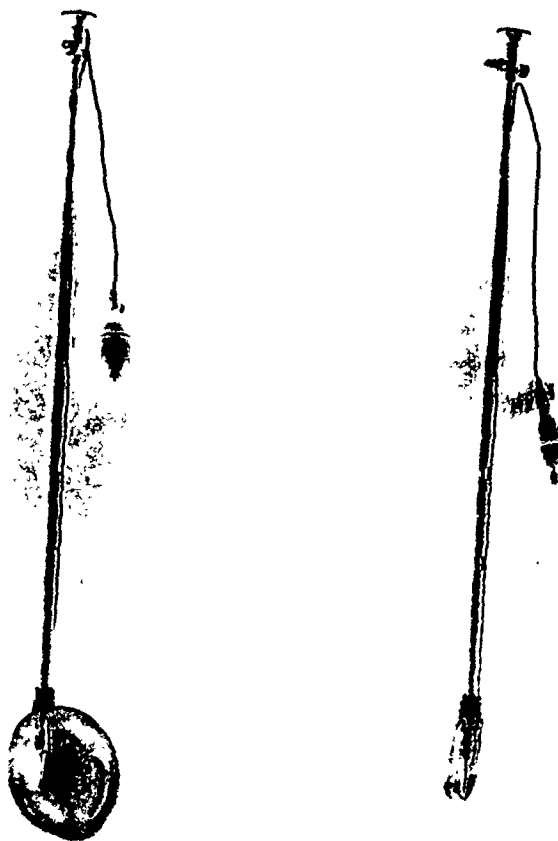


FIG. 2. Wolf-Schindler gastroscope with attachments: balloon, catheter and insufflation bulb. Lower balloon contains approximately 400 ml. of air.

two-thirds of the cases." The right lateral position has disadvantages and the majority of gastroscopists prefer the left lateral position. In the present paper a modification of the gastroscopic technic is presented in an attempt to obtain better visualization of the lesser curvature of the antrum. The stomach is distended by inflating a rubber balloon attached to the lower end of the gastroscope. In this way the lesser curvature is straightened.

METHOD AND RESULTS

During the usual gastroscopic procedure air is injected through several small openings, situated immediately above the objective, to separate the gastric walls. Small amounts of air are used to avoid discomfort,

regurgitation through the cardia and interference with peristalsis.

The following modification of the gastroscopic technic is suggested in order to obtain a more uniform distention of the stomach. A transparent rubber balloon is adapted to the tip of the gastroscope. The balloon covers the rubber finger, the electric bulb and the objective and is attached immediately above the latter. A non-collapsible tube is necessary for the insufflation and withdrawal of air. A ureteral catheter (Eynard No. 8) with a rubber extension is attached to the shaft of the instrument. The gastroscope is introduced in the usual manner and 50 ml. of air injected into the balloon. (Fig. 2.) After the usual gastroscopic examination more air is introduced into the

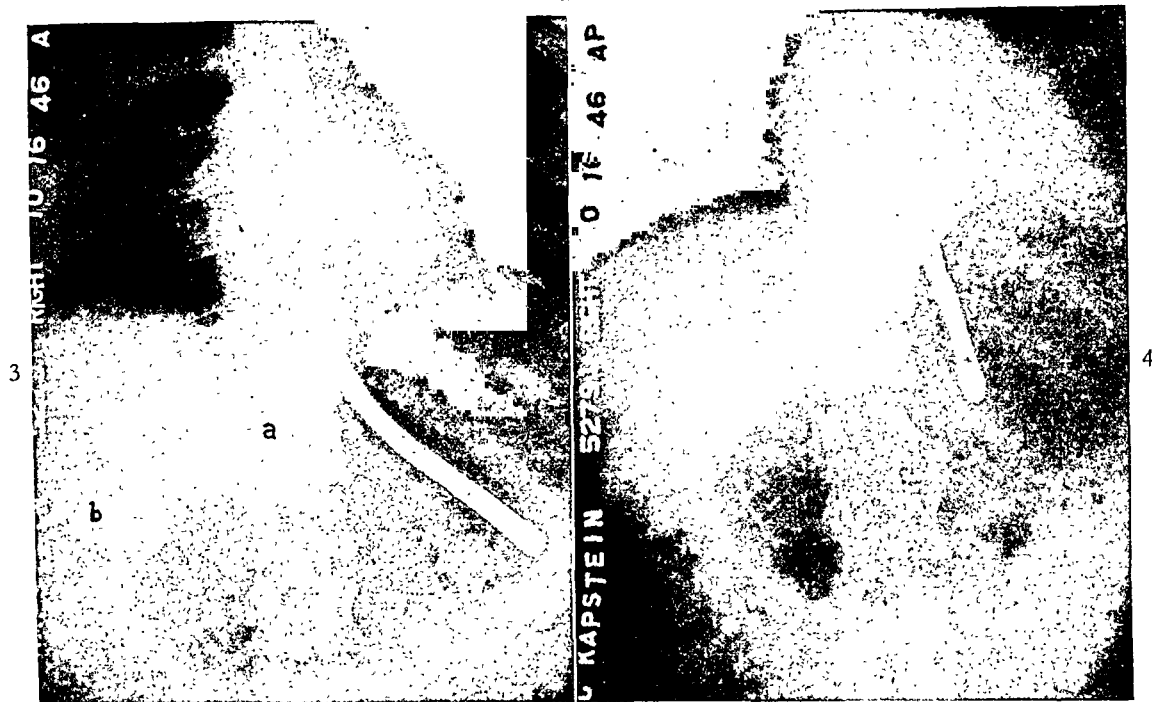


FIG. 3. Anteroposterior view of a stomach containing a balloon distended with about 800 ml. of air. Note the position of the angulus (*a*) and the duodenal bulb (*b*).

FIG. 4. Stomach distended with about 900 ml. of air; the lesser curvature is straight.

balloon. The stomach is sufficiently distended with about 500 to 800 ml. of air and becomes somewhat oval or spherical. The position of the pylorus varies with the amount of air and the degree of distention. By slowly withdrawing and rotating the gastroscope one can readily examine the antrum and then proceed upward to the corpus and fundus. The rugae are obliterated by this degree of distention but reappear when the balloon is partially deflated.

Figure 3 is a radiographic film taken in the anteroposterior position and shows the shape of the stomach containing a balloon inflated with approximately 800 ml. of air. The position of the angulus can be noted. There is a small amount of air in the duodenal cap.

Figure 4 represents a film taken with a larger balloon and a stomach tube kept semirigid by a wire in order to simulate a gastroscope. The stomach was distended

with about 900 ml. of air. The angulus is lifted by the balloon.

Although our experience with this method is still limited, the following points have been noted. The attachment of the balloon-catheter unit to the gastroscope does not add to the difficulty of introduction of the gastroscope. The lumen of the catheter being small, it is necessary to allow about one minute for the balloon to empty before withdrawing the instrument. The volume of air necessary to lift the angulus is approximately one-third to one-half the capacity of the average stomach and does not seem to add to the discomfort of the patient. The gastroscope can be moved around with ease in the inflated stomach. The bulb and the objective are always protected by the rubber balloon; there is less danger of causing a gastric burn by a hot bulb. This method avoids the changing of views caused by peristalsis and escape of air through the pylorus or cardia.

The color of the mucosa and the character of the rugae can be studied, either at the beginning or at the end of the examination, using very little air.

This method has been tested in thirteen patients. In all but one, the pylorus and the entire circumference of the antrum corpus were visualized, including the so-called blind areas A and B. (Fig. 1.) In one patient the pylorus was not seen and the angulus could not be lifted with the balloon containing about 800 ml. of air. This patient had a cholecystectomy for cholelithiasis and cholecystitis two years ago and at present has chronic myelogenous leukemia with hepatomegaly. These factors may have contributed to the failure of visualization of the pylorus.*

SUMMARY

The use of a transparent balloon attached to the lower end of a gastroscope is suggested for distention of the stomach. When inflated it straightens the lesser curvature and thus makes possible a more complete gastroscopic examination.

* Since submission of the manuscript fourteen additional patients were examined with this technic. The lesser curvature of the antrum and the pylorus were visualized in all fourteen cases.

The hitherto blind areas on the lesser curvature of the antrum and the posterior wall of the corpus were visualized in twelve of thirteen patients.

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Chemical Evaluation and Labeling of Protein Hydrolysates for Human Consumption*

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THE extensive use of protein hydrolysates in medicine and surgery and the fact that large quantities of these preparations are often administered creates a distinct need for exact knowledge of their composition.¹ The information given at present on the labels of many protein hydrolysates is insufficient. It is the purpose of this paper to call attention to this fact and to suggest measures designed to ameliorate the present situation.

METHODS

The following studies were undertaken on samples of ten different brands of protein hydrolysates. Total nitrogen was estimated by the standard micro-Kjeldahl method, ammonia by aeration according to Van Slyke² and creatine by Folin's auto-clave method.³ Total amino nitrogen was determined by five methods: (1) Nitrous acid method of Van Slyke;⁴ (2) Albanese's copper complex method;⁵ (3) formol titration (F_s) under conditions dictated by general considerations;⁶ (4) formol titration (F_w) according to specific conditions given by Winton⁷ and (5) free amino nitrogen by the ninhydrin method of MacFayden and Van Slyke.⁸ Sodium and potassium were estimated by flame photometry.⁹ Total phosphorus was determined by the method of Fiske and Subbarow.¹⁰

RESULTS

The compositions of the hydrolysates studied are given in Table I. It will be seen

that fairly large discrepancies occur in amino nitrogen content as determined by different methods. In most cases the method used in determining the amino nitrogen content given on the label of the product is not specified. The figures in column F_s represent, with one exception, the highest amino nitrogen values for a given product. Except for hydrolysates 3, 4 and 5, on which the label values for amino nitrogen are specified as having been obtained by the nitrous acid method, the crude formol figures (F_s) correspond most closely to label figures. Because of the danger of falsely high values due to interference by phosphates or constituents containing no amino nitrogen, the more refined formol titration figures (F_w) more nearly represent amino nitrogen.

One product, No. 10, which is sold and advertised as a protein hydrolysate, actually contains only 7 per cent of the nitrogen in the form of amino nitrogen, of this 2.3 per cent is in the form of free amino acids.

The ammonia and creatine values are reasonably uniform and low, the latter being somewhat high in those hydrolysates produced from animal sources.

The sodium content of the hydrolysates varied over a wide range. In at least one product (No. 6), sodium chloride has been added, presumably to improve flavor. The potassium and phosphorus contents were excessive in no samples and were frequently very low. The contents probably reflect those of the protein sources. The content

* From the Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. This work was aided by grants from the National Cancer Institute and the Teagle Fellowship Foundation.

of these minerals should be increased if the products are to be used as the sole source of protein.

COMMENTS AND SUMMARY

A study of the chemical composition of ten commercially available protein hydroly-

precautions, has been found reliable for many years in a variety of materials. Newer methods, such as that developed by Albanese, should be given more extensive trial before adoption as a procedure for establishing important food standards. Of the numerous colorimetric procedures, none is

TABLE I

CHEMICAL COMPOSITION OF TEN PROTEIN HYDROLYSATES AS INDICATED ON THE LABELS AND AS DETERMINED. ALL FIGURES ARE IN GM. PER CENT

No.	Source	Total Nitrogen		Creatine plus Creatinine	Ammonia	Amino Nitrogen†						Amino N Total N	Mineral Composition			Additions
		Determined	Label*			Cu	NO ₂	F _w	F _s	Ninhydrin	Label*		Na as NaCl	K	P	
1	Casein	12.0	12.0	0.06	0.46	6.4	6.0	6.5	7.3	5.7	7.5	0.50	0.5	Tr	0.5	0
2	Beef blood	11.0	11.0	0.07	0.24	6.3	5.1	5.7	5.8	4.4	6.0	0.46	0.6	0.1	0.4	0
3	Casein	12.8	13.0	0.04	0.27	4.4	3.1	3.5	3.5	1.6	3.0	0.24	3.1	Tr	0.84	0
4	Casein	12.9	13.0	0.02	0.12	3.4	3.1	3.0	3.6	2.3	3.0	0.24	5.3	Tr	0.85	0
5	Casein	12.9	13.0	0.03	0.11	4.4	3.1	3.1	3.4	1.7	3.0	0.24	2.9	Tr	0.84	0
6	Casein	8.9	...	0.16	0.16	3.8	3.2	...	3.2	2.3	...	0.36	21.0	0.6	0.9	Vitamins, iron, Ca, P
7	Lactalbumin	11.3	11.5	0.1	0.25	6.6	6.4	6.6	7.4	5.4	7.5	0.57	0.3	0.1	0.14	0
8	Brewers' yeast	11.5	11.5	0.2	0.12	2.6	4.0	4.3	5.9	...	6.0	0.35	4.5	2.3	2.2	B vitamins (natural)
9	Yeast, meat	6.6	6.8	0.15	0.21	2.9	2.8	3.0	3.2	2.5	3.6	0.44	0.4	2.4	1.3	Vitamins, carbohydrate
10	Beef, milk, wheat, yeast	7.5	7.2	0.32	0.10	0.5	0.5	0.7	0.8	0.3	...	0.07	4.8	1.7	0.74	Carbohydrates

* As labelled by manufacturer.

† As determined by the copper complex method (Cu), the nitrous acid method (NO₂), formol titration according to Winton (F_w), formol titration by usual technic (F_s) and by the ninhydrin method.

sates revealed that they vary widely in composition and that such variation is not always indicated by the labels. The application of a uniform method for the determination of the amino nitrogen content is recommended so that a direct comparison among the various products is possible. Since the only reason for producing a hydrolysate is to degrade the protein to more readily available constituents with a higher amino nitrogen content, the physician should be able to compare the commercial preparations in this respect.

The formol titration method was found to be unreliable for the determination of the amino nitrogen content because it seemed to be influenced by the phosphate content as well as by other factors. The best method for the amino nitrogen determination would at present appear to be the nitrous acid method. This method, used with proper

suitable since their application to a crude mixture yields unreliable results. The ninhydrin method determines the free amino acids present rather than the amino nitrogen content.

As a further safeguard against the use of ineffective medication, the biologic value of these preparations in man should be tested and expressed in standardized form. The wide variation of sodium chloride content in the hydrolysates studied indicates the desirability of a statement on the label of exactly how much salt any given product contains. If sufficient amounts of these products are given to supply 0.6 Gm. of nitrogen/day/Kg. during the postoperative phase, as has been recommended, excessive amounts of sodium chloride would be administered in some instances.

The content of other minerals, such as potassium, in these products should also

be indicated so that when they are used as the chief or exclusive source of nutriment the risk of depleting the patient of these minerals can be avoided.

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Use of Protein Hydrolysates by Mouth*

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THERE is at present much confusion regarding the indications for the use of protein hydrolysates as well as in the choice of the hydrolysate best suited for each clinical problem. It is not always easy from a perusal of the advertising literature to decide whether a product is a protein hydrolysate, an amino acid mixture or a protein concentrate. It is the purpose of this paper to clarify the situation regarding the administration of protein derivatives by way of the gastrointestinal tract.

Protein hydrolysates are obtained by the digestion of various proteins by chemical or enzymatic methods, i.e., by acid or alkaline hydrolysis or by the use of pancreatic or other proteolytic enzymes. In this manner the protein is broken down into amino acids of which the major part remain linked to each other in the form of di- or polypeptides, while a small fraction is present in the free state. A protein hydrolysate is thus clearly different from native protein, from protein concentrates and from mixtures of pure amino acids.

The preparation of amino acid mixtures and of protein hydrolysates represents a great advance in medical and surgical therapeutics, because such products have made possible intravenous feeding of the "building stones" of protoplasm in cases when parenteral nutrition is necessary; such treatment previously had been limited to carbohydrates, salt and fluids. The use of amino acid mixtures and protein hydrolysates *by vein* has been extensively studied and de-

scribed in the literature and will not be dealt with in this communication.¹ There are definite indications for *enteral* administration of these products; but their scope of useful application, while important, is more narrow than that claimed in some commercial advertising.

INDICATIONS FOR PROTEIN HYDROLYSATES

In some patients the protein of the diet should be supplemented. In these instances it is usually preferable to use protein concentrates rather than hydrolysates. In the presence of intact digestive mechanisms there is no reason to prefer hydrolyzed to native protein,^{2,3} except perhaps for smaller bulk. Furthermore, animal experiments seem to indicate that full proteins by mouth are twice to three times more effective than protein hydrolysates by vein.⁴

In a few instances protein hydrolysates provide the only means for the administration of proteins. Among these are cases of resection of the head of the pancreas for carcinoma of that organ, sometimes associated with inability to digest proteins, and cases of impaired protein digestion in chronic pancreatitis. Patients with ulcerative colitis sometimes benefit from protein hydrolysates and in some cases of mechanical rearrangement of the intestine with short circuits following surgery they may be the only means of protein nutrition. There are other specific indications, such as the use of protein hydrolysates for the treatment of gastric ulcer and pylorospasm,⁵ which will

* From the Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. This study was aided by grants from the National Cancer Institute and the Teagle Fellowship Fund for Cancer Research.

not be discussed here. In addition, one encounters situations when large amounts of protein can best be administered in the hydrolyzed form. This is the case whenever large losses of nitrogen occur at a time when the patient is unable to eat native protein, as during periods of serious infection or following operation, especially surgery of the gastrointestinal tract.

SPECIAL CONSIDERATIONS

The following special considerations will deal primarily with the use of protein hydrolysates in the postoperative phase.

The aim of protein therapy in general is the administration of sufficient protein (nitrogen) to obtain positive nitrogen balance. The nitrogen utilized serves to replenish deficient stores of tissue and circulating plasma proteins. It is apparently possible in certain instances to achieve positive nitrogen balance over a long period of time in hypoproteinemic patients without obtaining any increase in the amount of plasma protein.⁶ This emphasizes the necessity of following plasma protein regeneration directly, by measuring the circulating plasma protein levels instead of relying on the administration of "adequate amounts" of protein. Infusion of plasma may be necessary in addition to high protein feeding in order to restore plasma proteins to normal. The amounts of protein needed to replenish protein stores may be truly tremendous. Thus to insure optimal protein repletion in the postoperative phase as much as 0.6 Gm of nitrogen (3.75 Gm. of protein) per Kg. of body weight per day may be necessary.⁷ This is of the order of 200 to 250 Gm. of protein per day in patients of average weight.

When, based upon the preceding considerations, such large amounts of protein hydrolysate are being given, the practitioner must be certain that the product used will give the best possible results and will not be

toxic in such large amounts. In this connection it should be recalled that occasionally some hydrolysates may cause histamine-like reactions when given in large amounts. In at least one instance the administration of a hydrolysate (not now on the market) produced renal colic with the appearance of large amounts of urinary sediment, the nature of which was not ascertained.⁸

To assure optimal results some properties of the hydrolysates have to be considered and a certain basic knowledge of nutritional physiology has to be applied.

For instance, great losses of nitrogen will occur if large amounts of protein are being given unaccompanied by adequate amounts of energy sources such as carbohydrate and fat. In order to assure positive nitrogen balance these "protein spacers" have to be added. Such large amounts of carbohydrate in turn increase the demand for vitamins, especially those of the B complex, because of the catalytic rôle of these vitamins in carbohydrate metabolism and in the utilization of amino acids. A safe and reasonable daily vitamin supplement is the following:⁹

Vitamin C.....	500 to 1,000 mg.
Thiamine.....	20 to 40 mg.
Riboflavin.....	20 to 40 mg.
Niacin.....	150 to 300 mg.
Vitamin A.....	15,000 U.S.P. units
Vitamin D.....	1,500 U.S.P. units

The vitamin supplement can be given with the hydrolysate by tube or by mouth, unless there is known impairment of absorption from the gastrointestinal tract, in which case it must be given parenterally.

The amounts of minerals provided (usually well covered in normal diets of average composition) should be carefully considered when the entire protein intake, or most of it, is derived from hydrolysates, and even more so when energy is supplied as pure sugar and vitamins in their synthetic form. Normal average daily intakes of the various minerals are about as follows:¹⁰

Potassium.....	3.39	Gm.
Calcium.....	0.73	Gm.
Sodium.....	1.94	Gm.
Magnesium.....	0.34	Gm.
Phosphorus.....	1.58	Gm.
Sulfur.....	1.28	Gm.
Iron.....	0.0307	mg.

Adequate amounts of minerals are necessary when the replacement of lost protein

optimal daily requirement of normal individuals seems to be approximately 1 Gm. of protein per Kg. of body weight, whereas the requirement in the postoperative phase is considerably larger, about 0.6 Gm. of nitrogen (3.75 Gm. of protein) per Kg. of body weight. The protein requirement also varies with the degree of depletion. Elman has

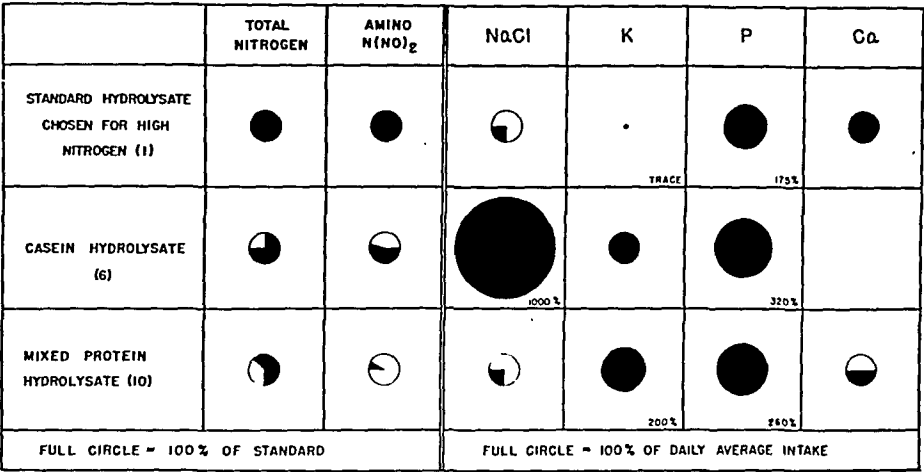


FIG. 1. Chemical composition of 350 Gm. of three different protein hydrolysates.

stores is intended, not only because of daily maintenance requirements but also to provide the building stones for the new protoplasm the organism is expected to build from the protein offered. Since potassium, phosphorus and sulfur enter the structure of protoplasm it is essential that all of these components be provided in addition to the amino acids and polypeptides. It is particularly necessary to supply potassium for intracellular fluid and sodium for extracellular fluid since there is no reserve store of these elements comparable to the stores of calcium, phosphorus and magnesium in bone. How widely the composition of different hydrolysates may vary with regard to nitrogen content and minerals is shown in Figure 1.

The actual amount of protein required by each individual patient can be determined accurately only by balance studies and measurements of plasma protein regeneration; it varies considerably. The

outlined a practical method for determining the protein requirements of depleted patients, based on the experimental work of Weech.¹¹ Elman's assumptions are as follows: (1) The normal plasma albumin value is 4.5 Gm. per cent; (2) the normal plasma volume is one-twentieth of the actual body weight; (3) the loss of 1 Gm. of plasma albumin is equivalent to the loss of 30 Gm. of tissue protein; (4) about 50 per cent of the ingested protein will be utilized and (5) 25 Gm. of protein are used for maintenance daily. The further assumption may be made that the total plasma protein deficit may be used as a criterion of depletion in those patients in whom it is not possible to obtain albumin values, since albumin usually comprises the bulk of the plasma proteins lost.¹¹ In this calculation a normal value of 7 Gm. per cent is assumed. The figures obtained from these calculations apply only to certain types of protein depletion and are at best only a rough guide for replacement therapy.

They will, however, fulfill the important service of illustrating that in most cases the amounts of protein needed are actually of a larger magnitude than is often realized. For example, a patient weighing 60 Kg. with a plasma protein of 5 Gm. per 100 ml. would have to be given 3,500 Gm. of protein to restore his tissue protein deficit. Twenty-five Gm. of protein would have to be added daily for maintenance while protein stores are being replenished.

Careful evaluation of a protein hydrolysate includes consideration of the biologic value of the original protein that was hydrolyzed, the bacterial purity and the lack of toxicity of the final compound.

In some commercial preparations, palatability is improved by the addition of salt. This may result in toxic doses of sodium chloride when enough of such a preparation is given to provide the full nitrogen requirement in the postoperative phase.

A study of the chemical composition of some protein hydrolysates now commercially available has shown that the information given on the manufacturers' label is often incomplete and that the methods by which it is obtained are not standardized. The importance of such factors and the inadequacy of present standards for protein hydrolysates have previously been discussed.¹²

DISCUSSION AND SUMMARY

The use of protein hydrolysates should be limited to cases with clearcut indications

such as have been outlined in the preceding paragraphs. They should be employed with full consideration of the physiologic implications of the use of such products. There is a wide variation in the composition of commercially available protein hydrolysates so that whenever large quantities are necessary a judicious choice of product is essential to avoid possible deleterious effects.

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Contributions of Right Heart Catheterization to the Physiology of Congestive Heart Failure*

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THE determination of cardiac output in man by the "direct Fick" principle and the registration of pressures in the heart and great vessels through the technic of right heart catheterization¹⁻⁴ have added significantly to the knowledge of the physiology of the human circulation, both normal and abnormal. This field is now under active investigation, with new observations constantly being made and ideas changing. It may be of interest, however, to review some of the work that has been done during the last five years and consider some of the points of view that have been developed. The present discussion will compare the normal circulation with that in congestive heart failure: first, with respect to pressure relations in the systemic and pulmonary circuits;⁵ second, with respect to total blood flow or cardiac output. Finally, these findings will be considered in relation to Starling's law.

The first of the facts to be established about the venous circulation in congestive heart failure through the catheterization technic was that the pressure gradient of 3 mm. or 4 mm. Hg which exists in the normal circulation between the peripheral

(arm) vein and right auricle diminishes as soon as the venous pressure begins to rise in right-sided failure, and peripheral and central pressures then become and remain equal as the congestive state progresses.^{6,7} This, as shown later by Ryder, Molle and Ferris,⁸ is due largely to the change in peripheral veins from the partially collapsed to the filled and distended state.

More detailed study of pressures in the great veins and right side of the heart, especially in relation to the events of the cardiac cycle and respiration, became possible with the application of pressure recording through the use of the Hamilton manometer.⁵

Figure 1 shows a series of normal tracings recording by optical registration: (1) the electrocardiogram, (2) femoral artery pressure (by a Hamilton manometer connected to an indwelling arterial needle) and (3) intracardiac pressures. Section A shows a right auricular pressure tracing; Section B, in its first half, shows a right ventricular tracing and Section C shows a right auricular tracing during moderately increased respiration, also an intrapleural recording of pressure changes during respiration.

The events of the cardiac cycle, as re-

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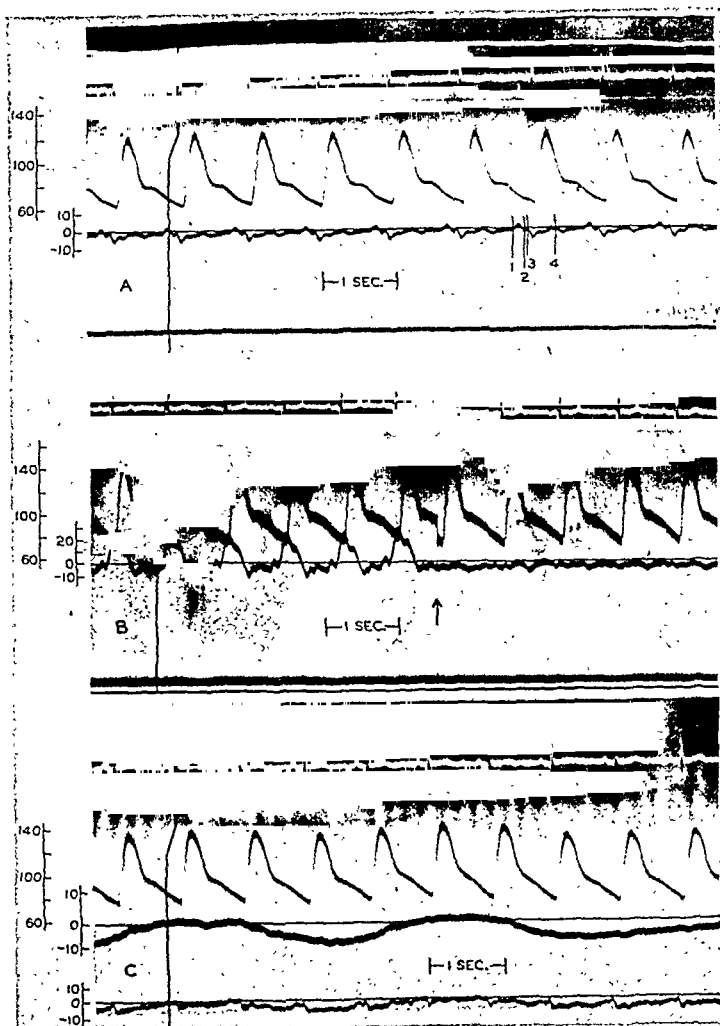


FIG. 1. Pressure tracings from normal human subjects. In Section A are recorded, from above downward, the electrocardiogram, arterial pressure tracing and right auricular pressure tracing. In Section B, electrocardiogram, arterial pressure and right ventricular pressure. At the arrow, the catheter tip was withdrawn from ventricle into auricle. In Section C, electrocardiogram, arterial pressure, intrapleural pressure (inspiration down, expiration up), right auricular pressure, during moderately increased respiration. The patient had a partial artificial pneumothorax.

corded in the right auricle, are indicated by the numbered lines. (Fig. 1, Section A.) At Line 1, auricular systole begins, producing a pressure 2 or 3 mm. Hg above the base line. Line 2 marks the onset of right ventricular systole, the slight upward notch in the pressure tracing probably indicating either bulging backward of the tricuspid valve or a momentary tricuspid insufficiency.⁶ At Line 3 a drop in auricular pressure begins due to

"descent of the base" of the heart, the heart moving forward with the ejection of blood headward; the auriculoventricular valve region moving toward the apex because of this motion and also because of ventricular contraction. Through the remainder of the ventricular systole and early relaxation, pressure in the right auricle builds up slowly as blood comes in from the great vessels. At Line 4 ventricular relaxation has reduced

pressure within this chamber to that of the auricle, the tricuspid valve opens with a drop in the auricular pressure as blood pours into the ventricle. From this point pressure builds up again gradually in the common auriculoventricular chamber, until the next auricular systole starts a new cycle.

As indices of the nature of blood flow in the great veins these tracings show that in the normal circulation under conditions of rest: (1) the basic pressure level is around zero (referred to atmospheric pressure); (2) the total pressure *change* during the cardiac cycle is small, about 5 mm. Hg. The fact that the great veins lose 70 or 80 cc. of blood with each ventricular filling and with so small a pressure change, indicates an ample venous reservoir under low tension.

Pressure in the right ventricle (Section B) usually shows a small rise due to auricular systole. Ventricular contraction then begins and maximum pressure is achieved rapidly. Since the normal diastolic pressure in the pulmonary artery is low, from 4 to 8 mm. Hg (as has been demonstrated with the catheter tip in the pulmonary artery⁶) the greater part of right ventricular systole is occupied with ejection of blood rather than with isometric contraction. Systolic pressure in the right ventricle (and in the pulmonary artery) in normal subjects varies from 18 to 30 mm. Hg and is on the average about 25 mm. Hg. The coarse vibrations in the tracings during the peak of systole (Fig. 1, B) are quite variable from one subject to another and may be artefacts. Right ventricular relaxation is also rapid, ending after opening of the tricuspid valve, in a small "diastolic dip," in which the pressure drops below the mean venous base line. After this, as already indicated, pressure builds up gradually in the common auriculoventricular chamber until the next auricular systole.

Figure 1, Section C shows the definite although small changes that occur in right auricular pressure tracings during moder-

ately increased breathing. The base line changes, although to a lesser degree than does the simultaneously recorded intrapleural pressure. The auricular pressure waves during the cardiac cycle also are greater during inspiration and less during expiration. A further study of this has been made with right ventricular and arterial pressure tracings by Lauson, Bloomfield and Cournand.⁹ Figure 2 gives the results in schematized form. It is found regularly in normal subjects that with inspiration right ventricular pulse pressure increases and femoral arterial pulse pressure diminishes. The reverse takes place during expiration. Furthermore, as already noted, the intrathoracic (intrapleural) pressure in inspiration decreases more than does the right intra-auricular or diastolic right intraventricular pressure. Thus the effective or net filling pressure on the right side of the heart is relatively increased. During expiration, intrathoracic pressure increases more than right intra-auricular pressure and net filling pressure is thus diminished.

If, as seems probable, these changes are responses to alterations in the volume flow of blood rather than vasomotor activity, then it can be calculated that with each inspiration more blood flows into the lungs from the right ventricle and less flows out of the lungs into the left auricle and ventricle; with the opposite changes in expiration. There are in some subjects small alterations in pulse rate with respiration but these do not significantly affect the general relation above stated.

The lungs thus act as a sponge in this dynamic equilibrium, taking in additional blood during inspiration and expelling it during expiration, a function clearly described many years ago by Thomas Lewis¹⁰ and by Sahlj.¹¹

If one modifies the principle of Starling's law to the extent of assuming that systolic output varies with diastolic filling pressure

in the ventricles (rather than with diastolic volume), then this respiratory equilibrium conforms with Starling's law.¹²

Additional evidence in favor of this explanation of the changes in right and left heart performance during respiration is pro-

phenomena of established failure and are not concerned with the mechanisms of its progressive development.

Figure 3, Section A, gives records of right intra-auricular and intraventricular pressures in a case of pure right-sided failure,

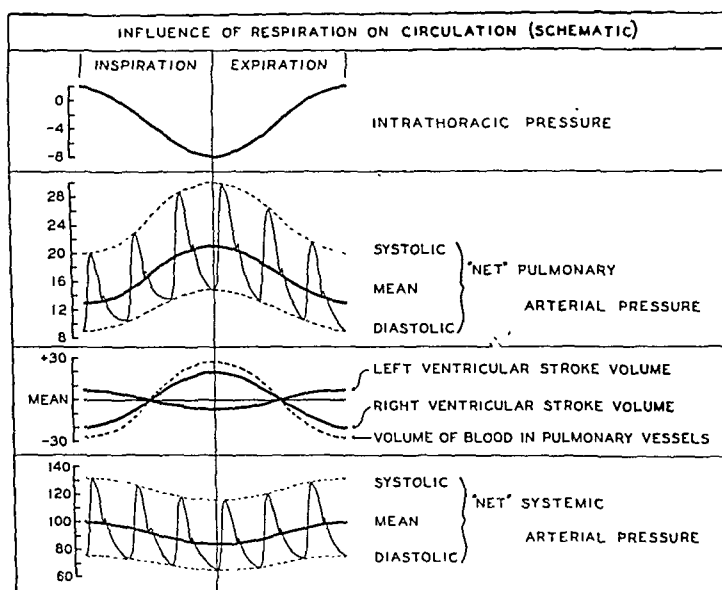


FIG. 2. (From Lauson, Bloomfield and Cournand.⁹) Schematized representation of right ventricular and arterial pressures as affected by respiration. With inspiration, right ventricular pulse pressures increase while femoral pulse pressures diminish; in expiration, the reverse occurs.

vided by the reverse effects noted during artificial respiration with a positive pressure respirator, as described by Motley et al.¹³ Inspiration produced by inflow of air under positive pressure results in a decrease in net filling pressure in the right heart with lowered right ventricular pulse pressures, while at the same time arterial pulse pressures increase, suggesting increased left ventricular systolic output. In (passive) expiration, right-sided net filling pressure and right ventricular pulse pressure increase while arterial pulse pressures decrease.

Pressure tracings from the great veins and chambers of the right heart in congestive failure present an interesting contrast to the normal records. It should be emphasized at this point that we are now dealing with the

specifically, a patient with constrictive pericarditis. It will be seen first, as one would expect, that the venous or right auricular pressure level is high, about 20 mm. Hg. In addition, the variations of pressure in the auricle during the cardiac cycle are much greater than in the normal subject, being as much as 15 mm. Hg. There are two sharp drops in pressure, one with the "descent of the base" at the time of ventricular ejection, the other with the opening of the tricuspid valve and inflow of blood from the auricle to the ventricle. Thus the pressure curve in the congested right auricle has a typical "W" contour. The whole response is what one might anticipate in a distended elastic vessel, with relatively small changes in volume producing large changes in pressure.⁸



FIG. 3. Arterial, right auricular, and right ventricular pressure tracings in a patient with right-sided congestive failure (patient had constrictive pericarditis).

As already mentioned, in cases of well marked right-sided congestion such as this one, mean pressures in the right auricle and peripheral veins are essentially identical. In fact, close measurement shows that during late ventricular systole and late auriculo-ventricular diastole, pressure in the right auricle is actually slightly above that in the peripheral (arm) vein⁵ and blood must, therefore, either be drifting slowly in the reverse direction in the great veins, or else a higher inflow pressure from other venous sources must be filling the right auricle with closure of the axillary venous valves.¹⁴ During the two sharp drops of the "W" there is an abrupt change of direction with a flow toward the heart.⁵

In Figure 3, Section B, the tracing of right ventricular pressure in the same case of constrictive pericarditis is shown. The systolic pressure is normal, there being in this case no disturbance in the lesser circuit.

Diastolic ventricular pressure is, of course, high and equal to auricular and peripheral venous pressure. A special feature is the marked ventricular "diastolic dip" as the ventricle relaxes just after the tricuspid valve opens, with a rapid rise again to its previous level. The explanation of this is the same as that of the second dip in the "W" curve of the right auricle.

Left-sided congestive heart failure produces greatly elevated pressures in the lesser circuit and the right ventricle. The degree of hypertension in the pulmonary circuit is seen in Figure 4, Sections A and B, a case of rheumatic heart disease with mitral stenosis and insufficiency and tricuspid insufficiency in advanced congestive failure. The right auricular tracing shows the high level of venous pressure and the large variations of pressure during the cardiac cycle already mentioned. The first dip of the "W" curve is absent in this case because of the tricus-

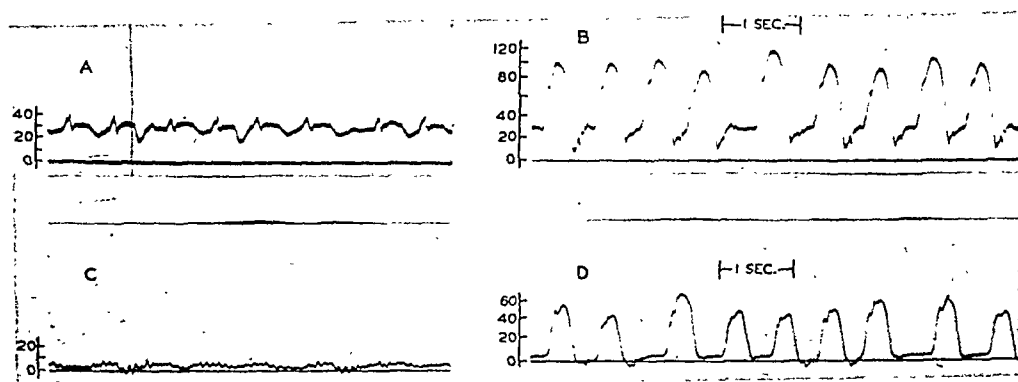


FIG. 4. Right auricular and right ventricular pressure tracings in a case of mitral stenosis. Sections A and B during congestive failure; Sections C and D after recovery of compensation.

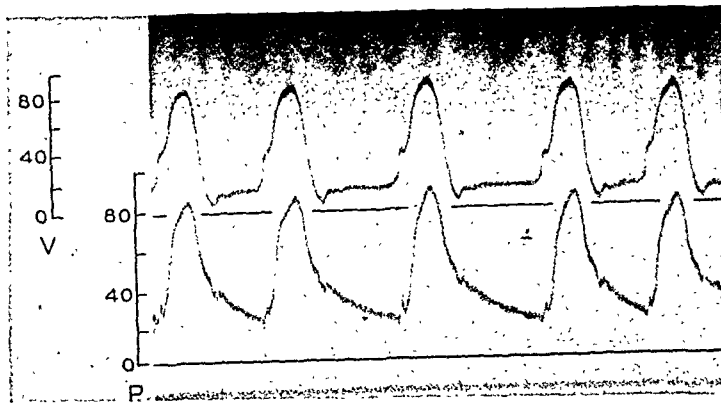


FIG. 5. Pressures in right ventricle (above) and in pulmonary artery (below), in a patient with rheumatic heart disease in left-sided and right-sided congestive failure. The tracings were taken simultaneously by the use of a double-channel catheter. The recording membrane for the pulmonary artery pressure tracing is slightly more sensitive than that for the right ventricle.

pid insufficiency.⁵ Auricular systole is absent and the heart rate irregular since the auricles were fibrillating.

Even more striking, however, is the right ventricular tracing, with systolic pressures up to 100 mm. Hg. Figure 5, a record of pulmonary artery pressure taken from another case with the catheter tip in the pulmonary artery, shows that the diastolic as well as the systolic pressure in this vessel is elevated. This four-fold increase in systolic pressure in the lesser circuit demonstrates beyond any question that hypertensive congestion in the lesser circuit is the dominant factor in left sided congestive failure, thus confirming the *Lungenstarre* postulated by von Basch more than sixty years ago.¹⁵

In Figure 4, Sections C and D, tracings of the same patient after digitalization and partial recovery of compensation are reproduced. It will be seen that the systemic venous pressure has returned to normal. The pulmonary arterial hypertension is less but the systolic pressure in the lesser circuit is still about twice normal.

In *cor pulmonale*, or right sided cardiac hypertrophy associated with chronic pulmonary disease, pulmonary arterial hypertension is an important factor but it is

interesting that the degree of this hypertension is usually less than that seen in left heart failure of the congestive type.⁵ There is, however, an additional disturbing factor caused by the loss of pulmonary elasticity. In Figure 6 arterial and right ventricular pressure tracings in a group of patients with emphysema and various forms of chronic fibrotic pulmonary disease are shown. Section A is from a patient with emphysema. The variations of auricular pressure due to inspiration and expiration are somewhat greater than the normal range but there is no right ventricular or pulmonary hypertension. In nineteen cases of emphysema studied by Bloomfield et al.,⁵ five had normal right ventricular pressures. The other tracings in Figure 6 illustrate increasingly severe degrees of chronic fibrotic pulmonary disease with *cor pulmonale*. None of these patients, however, were in right sided congestive failure. In addition to pulmonary arterial hypertension there will be noted, as pulmonary elasticity becomes impaired and ventilatory effort increased, a progressive exaggeration of the normal respiratory pressure effects on inflow and outflow of blood to and from the lungs. The basic levels of venous pressure shift widely with

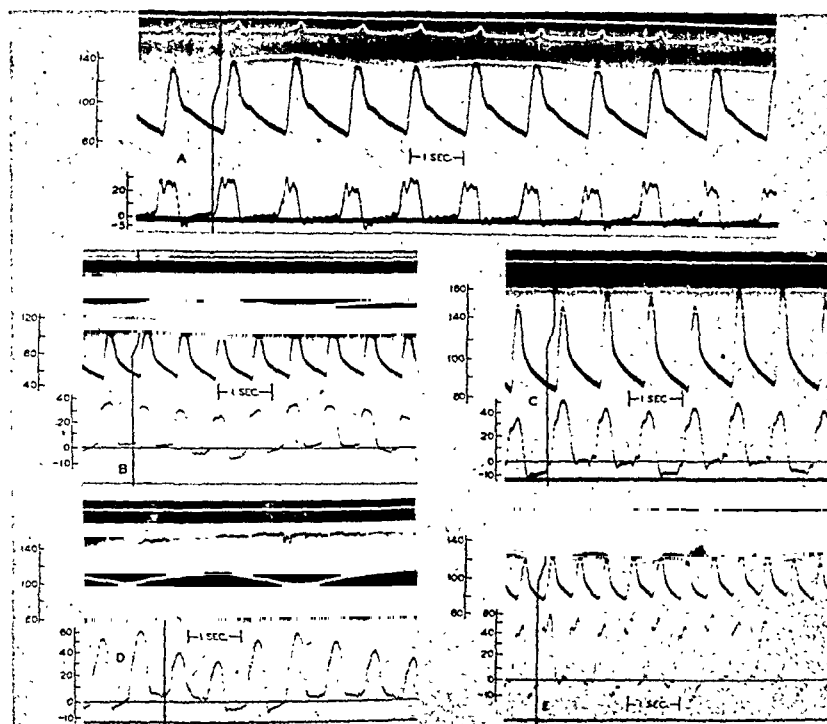


FIG. 6. Arterial (middle curves) and right ventricular (lower curves) pressure tracings in five subjects with pulmonary emphysema and varying degrees of pulmonary arterial hypertension. The white lines above are records of respiration: inspiration down, expiration up.

respiration, as do the amplitude of right ventricular pressures and femoral arterial pulse waves, indicating alternate filling and emptying of the pulmonary vascular bed with inspiration and expiration. Whether this imposes a further strain on cardiocirculatory function cannot be said with certainty but it seems not unlikely. It might be noted that patients with left heart failure and pulmonary engorgement may also show these marked respiratory variations in intracardiac pressures.

Rist¹⁶ noted a relative decrease in amplitude of cardiac systole during inspiration in such patients but explained the effect as a decrease in inspiratory systolic outflow of both right and left ventricles, associated with a rigid pulmonary vascular bed. It is suggested that the change in amplitude of the heart shadow, as observed by Rist, may have been largely due to the left ventricle and that while the pulmonary vascular bed

in these cases may be less elastic than normal, it is relatively more elastic than the pulmonary parenchyma so that the exaggerated effort of inspiration and expiration produces alterations in vascular volume that are greater than normal.

In cor pulmonale with right-sided congestive failure the pressure changes in great veins and right heart chambers during the cardiac cycle are similar to those already described.

All the above evidence taken together gives emphasis to the importance of pressure disturbances in both systemic and pulmonary circulations in congestive heart failure.

Turning now to a consideration of total blood flow or cardiac output, one may present the essential findings briefly.

In normal adult subjects at rest, the average cardiac output as determined by the catheterization procedure is about 3.1 liters per square meter of body surface per minute,

or 5.4 liters per minute for an individual of average size.¹ As was demonstrated by earlier technics (Grollman¹⁷) cardiac output is an extremely labile function, often changing markedly with nervousness or anxiety.¹

The response in normal subjects to rapid

TABLE I
PATIENT A. R. ARTERIOSCLEROTIC HEART DISEASE, HYPERTENSION AND PROGRESSING CONGESTIVE HEART FAILURE

Date	9/21/43	1/18/44
Cardiac index, liters	2.33	2.01
Stroke volume, cc	44	30
Arteriovenous difference, cc./100	5.2	7.4
Arterial blood pressure, mm. Hg.	154/89	190/129
Peripheral resistance	2570	3335
Auricular pressure, mm. H ₂ O	+24	+140
Arm venous pressure, mm. H ₂ O	+35	+135
Right ventricular pressure, mm. Hg.	27/4	64/18
Plasma volume, cc./sq. m.	1420	1620
Hematocrit	40	40
Total blood volume, cc./sq. m.	2370	2700

increase in venous inflow by intravenous infusion and the response to reduced venous inflow by venesection or by applying venous cuffs to the extremities have been variously reported. According to McMichael and Sharpey-Schafer,¹ cardiac output is regularly increased in proportion to the increase in inflow pressure or pressure in the right auricle, and correspondingly decreased as the right auricular pressure decreases with venesection or venous cuffs. Warren, Brannon, Stead and Merrill, however,¹⁸ in similar experiments, have not found this correlation and believe that in normal circulations alterations in cardiac output may be independent of pressure in the right auricle (i.e., diastolic filling pressure in right auricle and right ventricle).

Since Starling's law states that the energy of systolic ejection of the heart varies with diastolic filling or diastolic size, it is of interest to inquire how the heart size changes with increased output. McMichael¹⁹ has shown a definite increase in the cardiac

area by x-ray during a rapid intravenous infusion, associated with increased output.

In muscular exercise, on the other hand, Nylin's recent work²⁰ indicates that increased stroke volume is achieved wholly by increased emptying of the heart chambers, the cardiac size being smaller than when at rest. Measurements of cardiac output during exercise, by the catheterization technic, are in progress in several laboratories but have not yet been published.

The subject of cardiac output in congestive heart failure has been extensively studied, both before and since the introduction of right heart catheterization. Harrison, in his important monograph published in 1935,²¹ summarized previous investigations and added evidence from his own experiments, indicating that decrease in cardiac output is not present early in the development of congestive heart failure. The validity of this position is now being examined again with the catheterization technic.

In patients with fully established congestive failure, however, the following facts have recently been established, both in Cournand's laboratory²² and by McMichael and his group:²³

(1) There are some types of congestive failure regularly associated with decrease in cardiac output, notably arteriosclerotic heart disease and rheumatic heart disease. Table I gives figures in a typical case of the former, first in mild failure and later when cardiac insufficiency was advanced. The cardiac index, or cardiac output in liters per minute per square meter of body surface, was in this case well below the average normal value of 3.1, and fell still further with further decompensation.

(2) There are other forms of congestive heart failure associated with a normal or increased cardiac output, even when the congestive state is marked. In such clinical conditions there is usually some metabolic

or mechanical dysfunction which induces or stimulates the increased output. These conditions and their corresponding metabolic dysfunctions are as follows:

(1) Anemia (low oxygen transport per unit of blood); (2) cor pulmonale (usually

however, there are two prior questions which have been raised in other discussions of these findings and should be considered:

(1) Can one say that a state of cardiac failure exists at all, so long as cardiac output is maintained?

TABLE II
MEASUREMENTS OF THE CIRCULATION IN A GROUP OF SEVEN PATIENTS WITH RHEUMATIC HEART DISEASE IN FAILURE AND IN A GROUP OF SIX PATIENTS WITH COR PULMONALE IN FAILURE

	Rheumatic		Cor Pulmonale	
	Average	Range	Average	Range
Cardiac index, liters.....	1.85	(1.21-2.65)	3.45	(2.59-4.88)
A-V difference, cc./100.....	8.1	(6.4-11.4)	4.6	(3.4-5.9)
Peripheral resistance.....	2562	(1710-3720)	1342	(1100-1510)
Auricular pressure, mm. H ₂ O.....	+240	(167-350)	+114	(-24 to +180)
Venous pressure, mm. H ₂ O.....	+245	(173-320)	+126	(-15 to +222)
Ventricular pressure, mm. Hg.....	100	(81-117)	53	(35-81)
Plasma volume, cc./sq. m.....	2574	(1630-3370)	1685	(1400-1860)
Hematocrit.....	45	(36-53)	63	(54-69)
Arterial O ₂ saturation, %.....	95	(90-98)	71	(61-85)

a low arterial and tissue oxygen tension); (3) thyrotoxicosis (increased oxygen consumption); (4) arteriovenous communications (increased venous return); (5) Paget's disease (essentially arteriovenous communications in vascular bed of affected bones); and (6) in addition, Burwell et al.,²⁵ have recently shown a very large cardiac output (11 liters per minute) in a case of beriberi heart disease in marked congestive failure.

Table II gives average figures of cardiac output and other functions in a series of cases of cor pulmonale, compared with similar measurements in cases of rheumatic heart disease, both groups of patients being in congestive failure.

These clearcut findings would seem to lead to an equally definite conclusion; that in the state of established congestive heart failure, cardiac output may be high, low or normal, or to put it otherwise, that a lowered cardiac output is not an essential feature of this condition.

Before this conclusion can be accepted,

(2) In cases of the congestive state with cardiac output at levels that are normal or above, to what extent is the congestion in its various aspects compensatory, maintaining cardiac output higher than it would otherwise be, to the benefit of the individual?

These are essentially different aspects of the same question, the first being an extreme or limiting case of the second.

It ultimately becomes a matter of terminology as to whether the advanced congestive state with normal cardiac output shall be called heart failure or not. It is difficult to see, however, why it should not be so called. The state of the heart, emptying inadequately, greatly dilated and under excessive filling pressures, is certainly one of profound distress. Furthermore, if the condition continues to progress, failure becomes complete and the patient dies. Surely this is a form of heart failure. It happens to be failure in terms of pressure relations rather than of flow relations.

These recent observations, in fact, do not

alter Harrison's excellent description in his monograph of 1935,²¹ of the development of the congestive state with incipient failure of cardiac emptying, then dilatation, this resulting in maintained cardiac output, then further failure of emptying with increased diastolic (i.e., venous) pressure and so on through the successive steps of decompensation. Clinically, one should look for the onset of true heart failure earlier rather than later in this train of events.

Since the constant disturbances in congestive heart failure are those of pressure rather than of flow, the term "congestive" is both appropriate and adequate. One may question, however, whether the terms "backward" and "forward" failure are any longer useful or accurate. It is true that the cardiac chambers are dilated in failure and that inadequate emptying of these chambers is a part of, if not a cause of, the general state of venous congestion, but if blood is still moved around the circuit in a normal amount the condition is not backward failure from the point of view of flow. If it is backward failure from the point of view of pressures only, then we have simply returned to the status of congestion, from which our argument started.

It is perhaps not too much of a digression to note that the term forward failure, to describe states of shock due to peripheral circulatory failure, also becomes difficult to apply satisfactorily, in view of present knowledge of the circulation in different forms of shock.²⁶ Is the forward failure a failure of blood flow or of pressure? There are states of shock with low blood flow and low arterial pressure (trauma and blood loss), others with low blood flow and normal or increased arterial pressure (burns) and still others with normal blood flow and low arterial pressure (syncope). All, however, are associated with inadequate filling of one or another part of the system of heart and great vessels. Perhaps, instead of forward

versus backward failure, better descriptive terms would be depletion versus congestion of all or part of the system: veins plus heart plus arteries.

The question already presented above as to whether the congestive state may at times

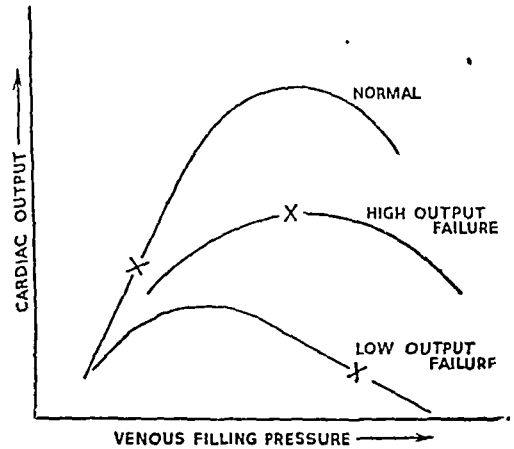


FIG. 7. (From Howarth, McMichael and Sharpey-Schafer.¹⁴) Suggested filling pressure-cardiac output curves for normal subjects and cases of high and low output failure. Crosses represent usual states of each group at rest.

be a favorable compensatory mechanism, demands a critical review of the physiologic principle upon which modern ideas of cardiac output rest, namely, Starling's law, and the extent of its applicability to the human circulation in the light of these recent observations. In its most simple terms this law (derived from studies with the heart-lung preparation of the dog) states that the energy of cardiac ejection (or output) increases in proportion to the length of the heart muscle fibers, in other words, to the diastolic volume of the heart chambers; up to a certain degree of filling, beyond which further overfilling results in decrease rather than increase in cardiac output. The upper curve in Figure 7, from the recent paper by Howarth, McMichael and Sharpey-Schafer²³ gives the essential relation, although using diastolic filling pressure rather than diastolic volume as the abscissa.

To what extent does the normal circulation obey Starling's law? McMichael's data on intravenous infusions and venesection,¹ are consistent with the law, cardiac output increasing along with increased filling pressure and increased heart size. On the other hand, in muscular exercise although venous pressure, cardiac output and stroke volume increase, cardiac size apparently diminishes (Nylin²⁰). Stead's data on venesection and anxiety states^{1,18} also do not fit Starling's law. McMichael¹ has at least one observation that does not; epinephrine given intravenously in doses of 3 micrograms per minute increases cardiac output with no change in venous pressure or pulse rate. In favor of Starling's law is the well known fact that during severe physical training, such as that of oarsmen training for a race, cardiac size increases.

Apparently, therefore, while there is a tendency in the normal circulation to follow Starling's law, there are also influences of nervous or metabolic origin which may alter such functions as cardiac tone (diastolic heart size at a given inflow pressure) or systolic emptying and thus modify cardiac performance outside this law.

There are other influences acting in the same manner. The increased blood flow, for example, seen in anxiety states, fever, moderate thyrotoxicosis or anemia *without* congestive failure usually occurs with both normal venous pressures and little or no increase in heart size and is thus dependent on mechanisms other than those of Starling's law.

Whether normal hearts pushed to the point of failure dilate with falling output (Fig. 7) is not certainly known but such is probably the case. Extreme overexertion is known to produce cardiac dilatation in normal subjects.

There is abundant evidence, however, that the heart in congestive failure that has a low output occupies a position indicated by

the "low output failure" in Figure 7. The heart is dilated, the venous pressure is high and the output is low.²³ Proof that such a heart is overdilated, that it is on the descending limb of the curve (mark "X" on the lowest curve), is given by the fact that decrease of venous pressure, as by cuffs, digitalis or phlebotomy produces prompt increase in cardiac output.

The low level of cardiac output at which these hearts are operating, as compared with the normal, is presumably associated with the fact that for the most part these are hearts with intrinsic myocardial damage.

Is it also true that these hearts were at an earlier stage on the rising side of the curve when increased venous pressure and increased diastolic volume were associated with a favorable compensatory increase in cardiac output? It is difficult to answer this question. Clinically, cardiac dilatation is usually considered an unfavorable event and the sooner it is reduced the better the clinical result. In any case, as in so many forms of compensation in a failing organ, the compensation soon becomes unfavorable. In this instance abnormal pressure relations become a greater handicap than the increased cardiac output is a benefit and all the evils of congestive failure supervene.

The cases of "high output failure," represented by the middle curve in Figure 7, bring forward more clearly the question of a compensatory state of congestion. In the cor pulmonale group, for example, it is McMichael's suggestion that the venous pressure elevation and correspondingly increased diastolic filling has increased the cardiac output to a maximum (point "X" on the curve). In support of this he notes that digitalis decreases both venous pressure and cardiac output in such hearts and is known to be an ineffective drug clinically.

On the other hand, the lowering of venous pressure may not be unfavorable in such patients. Table III, for example, gives figures

in a case studied by Cournand of cor pulmonale in right heart failure, in which a normal cardiac output was further increased after phlebotomy and the patient dramatically improved. In general it has been our experience that patients with cor pulmonale

TABLE III

CARDIAC OUTPUT BEFORE AND AFTER A PHLEBOTOMY OF 1,200 CC. IN A PATIENT WITH COR PULMONALE AND CONGESTIVE HEART FAILURE

Patient M. K., 10/5/42	Before Phlebotomy	Immediately after	Three Hours after
Pulse rate	92	93	97
Venous pressure, mm. H ₂ O	185	84	
Right auricular pressure, mm. H ₂ O	185	64	115
Arterial pressure, mm. Hg.	154/100	137/82	133/81
Arterial oxygen saturation, %	61	73	60
A-V oxygen difference, cc.	49	44	41
Cardiac index, lit./min./sq. m.	3.1	3.4	4.0
Plasma volume, cc.	3310	3100
Hematocrit, %	68		63

in right-sided congestive failure have large blood volumes and are greatly improved by repeated venesections. In our patients, therefore, while cardiac output is high in the presence of venous congestion the latter is still a phenomenon of failure and its relief results in an improved circulation.

There is also the evidence (Sharpey-Schafer²⁷) in favor of a compensatory increase in blood flow due to venous pressure increases in patients with severe anemia and congestive failure. It should be noted, however, that severe anemia regularly causes increased cardiac output, even without venous pressure increase;²⁸ also that normal hearts can increase cardiac output as high as it occurs in anemia without the development of congestion. Therefore, when the congestive state develops in anemia, even if it is compensatory, it is the compensating response of a failing heart and not the response of a normal heart.

By way of summary, so far as concerns the

application of Starling's law to the human circulation, the following comments are suggested:

(1) In normal subjects, in certain restricted measurements under controlled conditions, a relation at least between cardiac stroke volume and diastolic filling pressure can be demonstrated in accordance with Starling's law; (2) in other physiologic situations, such as exercise, anxiety, etc., other influences affect cardiac performance outside the scope of Starling's law and (3) in congestive heart failure, the law does apply in the "failure" range or descending segment of the curve, with cardiac output increasing as venous pressure and heart size are diminished.

Starling's law, in fact, applies to the human circulation about as well as one could expect of a physiologic principle developed from the performance of a heart-lung preparation; the more the human heart is exposed to and reacts to nervous, vasomotor and metabolic influences the less it behaves in accordance with this law; the more the heart fails to respond to such influences and becomes simply a pressure-volume muscle preparation, as in congestive failure, the more closely it follows the law.

From this point of view, Starling's law becomes a useful but not exclusive and not always dominant principle to be considered in the interpretation of normal and abnormal circulatory states. One further comment might be made, namely, that the current practice of describing Starling's law as a relation between cardiac output and diastolic filling pressure may prove to be more useful than the original law which states the relation between cardiac output and diastolic heart volume. If cardiac tonus is an important factor, the relation to diastolic filling pressure may even be more accurate.

A number of important studies have been made with the catheterization procedure of

other aspects of congestive failure—the early development of the congestive state, the relation of renal blood flow, and the action of digitalis and other drugs on the heart and peripheral circulation. These are outside the restricted scope of the present discussion.

SUMMARY

1. Some observations are presented of intravascular and intracardiac pressures, and of cardiac output in subjects with normal hearts and in patients with congestive heart failure, as obtained by the technic of right heart catheterization.

2. The phenomenon of congestive heart failure is essentially a disturbance of pressures rather than of blood flow.

3. There appear to be limitations in the applicability of Starling's law to functioning human hearts.

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Seminars on Thromboembolism

Anticoagulation Therapy with Heparin/Pitkin Menstruum in Thromboembolic Disease*

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THE purpose of this report is to present experimental and clinical data regarding the rationale and effectiveness of heparin in the treatment of thromboembolic disease, and to describe in detail an improved and accepted method of prolonged heparinization which is safe, practical and simple.¹⁻⁸

Heparin/Pitkin menstruum has been for a number of years the subject of elaborate clinical study and trial in the prophylaxis and treatment of intravascular thrombosis.^{2, 3, 5, 6, 8, 9, 10, 11} Our composite series totals more than 400 patients who received several thousand subcutaneous deposits of heparin/Pitkin menstruum. Inasmuch as experimental study and clinical experience with this anticoagulation preparation has been more extensive in the field of venous thromboembolism, this division of thromboembolic disease will be considered in detail. The knowledge thus acquired has provided the basic principles which are applied in the treatment of arterial thrombotic diseases. The studies and investigations of anticoagulation therapy in arterial thrombotic disorders, some of which are still in the exploratory stage, will also be reviewed.

VENOUS THROMBOEMBOLIC DISEASE

Although much of the discussion on the functional pathology of venous thromboembolic disease has been published in

previous papers,^{3, 5, 12, 13} reiteration of certain basic information and findings is desirable if not indispensable. Despite the fact that thromboses in the calf and plantar veins were observed for many years and were not regarded as uncommon or rare, the relationship between these minimal thrombotic episodes and fatal pulmonary emboli has been emphasized only in the past decade. During this period the anatomic development of pulmonary emboli has been elucidated by Rössle,¹⁴ Neumann¹⁵ and Frykholm.¹⁶ At the same time the clinical and radiographic criteria by which aseptic deep calf thrombi can be recognized even in their incipency and prior to the occurrence of pulmonary embolization were established by Homans,¹⁷ and Bauer,¹⁸ Bancroft,⁹ Ochsner,²⁰ Allen and his co-workers²¹ and Bauer²² during this same period defined the principles of treatment for pulmonary embolization based on functional anatomy and clinical pathology.

It is fitting at this point to trace the functional pathology of a venous thromboembolic accident, keeping in mind, however, there are many gaps in our knowledge of spontaneous intravascular clotting. Our interest in the genesis and nature of intravascular clots was stimulated during an investigation of experimental human frostbite.^{12, 13} A study of the train of events in this condition by Greene²³ and Rotnes and

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Kreyberg²⁴ revealed that there is clumping of erythrocytes in the dilated arterioles for at least seventy-two hours after exposure. This clumping has been attributed to loss of plasma through the highly permeable vascular wall. As a result the red cells are stranded, "silting" up the blood vessels and forming what may be termed a sludge. Related and revealing information on sludge development may be found in Knisely's report on this phenomenon in the blood during malaria and in traumatic shock.²⁵ He and his co-workers observed that the red cells become agglutinated and form small clumps as a result of which the blood flow becomes sluggish and generalized thromboses supervene.

Another related circumstance is the well established fact that the blood platelet count rises rapidly in the immediate postoperative period and that the platelets become hyperadhesive.^{26,27} Both phenomena attain their maxima about the tenth day after operation. In addition to changes in the number and properties of the blood platelets and sludge formation, the postoperative period is characterized by variable hemoconcentration, enhanced viscosity of the blood plasma, hyperglobulinemia and an increased content of fibrinogen in the blood. Since all of these changes contribute to clot formation the stage is set for intravascular thrombosis anywhere in the body.

Even though all of the component elements for clot formation are present, the catalyzing circumstance which initiates the chain reaction eventuating in clot formation is still unknown. In a statistical review of phlebothrombosis one suggestive fact emerges: that a common denominator may be venostasis, whether due to angulation, actual obstruction or increased venous pressure secondary to either obesity or cardiac insufficiency. If one now considers what part of the body would be most subject to slowing of the blood stream, for self-

evident reasons the lower extremities must rank first. Thus during the postoperative period, in the presence of chemical and physical changes in the blood, minimal intimal trauma in a venule of the lower extremity may well initiate local intravascular thrombosis.

The primary thrombotic process usually starts in the smaller vessels in the muscular portions of the calf and less frequently in the plantar veins. The clot progresses and soon reaches a larger vessel into which it extends and grows. At first the clot is attached only to the venule and later engages the wall of the larger vessel. During the stage of propagation it is, in the main, a red cell clot which waves freely in the vascular stream. This clot contains minute amounts of fibrin and is but one stage removed from the sludges observed in experimental frostbite and malaria.

The red cell clot has been produced by us in the laboratory;^{4,7} a palpable, visible clot which, however, is so loosely put together that it disintegrates readily. As the clot grows the propagating proximal end includes all of the stages just described. It is now that the clot is most dangerous for it may separate at any time, either spontaneously or due to muscular exertion such as straining at stool or getting out of bed. If the clot does not become detached, it is slowly organized and becomes agglutinated to the blood vessel wall. During the stage of clot propagation, immediately adjacent tributaries and collaterals are also involved so that when organization with either obliteration or recanalization occurs, there is a shunting of the venous stream to superficial vessels incapable of bearing the burden. This bizarre venous shunting is readily seen in post-thrombotic phlebograms. (Fig. 1.) Although we have been discussing so-called aseptic phlebothrombosis, essentially the same processes occur in infective thrombophlebitis in which the

most proximal portion of the clot resembles the non-infective type despite the fact that the distal clot is for the most part attached to an injured intima.

If either the aseptic or septic type of thrombophlebitis be of prolonged duration, a periphlebitis occurs which involves the adjacent perivenous lymphatics. Since lymphatic fluid is also capable of coagulating it is quite conceivable that postphlebitic edema may be due in great part to consequent obstruction of the return lymphatic flow of an extremity.

Rationale. Termination of the progression of the thrombotic process is the ideal objective and, to the best of our present knowledge, the anticoagulants appear best suited for this purpose. The properties of heparin which render it uniquely applicable in thromboembolic disease are that it prevents (with the aid of a plasma co-factor) the conversion of prothrombin to thrombin; it forms with serum albumin a strong anti-thrombin and finally, it prevents the formation of thromboplastin from platelets. (Fig. 2.)

Heparin is a mucoitin polysulfuric acid. The most potent preparations of heparin, according to Jorpes,²⁹ contain 45 per cent sulfuric acid, which results in an exceedingly strong negative electric charge. No other compound of high molecular weight in the mammalian body has such a strong electric charge. Apparently heparin exerts its action through this charge. This seems to be supported by the neutralizing effect of basic protamine, which has the property of promptly counteracting the action of heparin. The multiple effect of heparin on thromboplastin, prothrombin, thrombin, the hemolytic complement, iso-hemagglutinins and different enzymes is most readily explained as a loading and unloading of electric charges on the proteins concerned. The properties of heparin predicate the fact that a clot, regardless of its



FIG. 1. Phlebogram taken five months following femoral thrombosis treated merely by paravertebral nerve block. Observe the failure of visualization of deep venous channels and the bizarre shunting to the superficial venous system due to the post-thrombotic occlusion of the femoral vein.

site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

The acknowledged failure of heparin to act on the preformed *in vitro* clot is readily demonstrable.³⁰ However, the preformed *in vivo* clot has on occasion been seen to disappear. This startling contrast between *in vivo* and *in vitro* action has stimulated us to determine, if possible, the precise action of heparin in the living organism. For this study a method of experimental induction of thrombosis in the rabbit was devised which fulfilled all the requirements and which was uniformly successful.⁴

It has been possible to determine experimentally in animals at what stage of clot

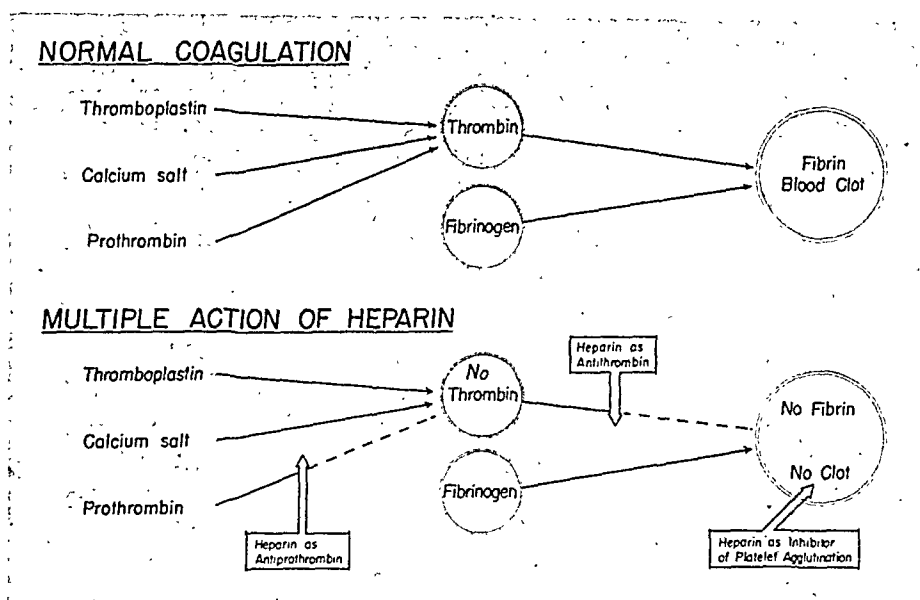


FIG. 2. Graph portraying the mechanism of anticoagulant action of heparin.

formation heparin administration results in solution of the clot and what effect heparin has on the organizing clot.^{5,7} In all of the experimental animals heparinization was accomplished by the subcutaneous administration of heparin/Pitkin menstruum, the treatment program being conducted in a manner comparable to that in humans.

Briefly, studies on the effect of heparin in experimental venous thrombosis in the rabbit have yielded the following data:

(1) Red cell clots not organized and containing a minute amount of fibrin (sludge stage) disappear completely under heparin therapy. (Figs. 3 to 8.)

(2) Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. These compensatory collaterals often become as large as the originally occluded vessel. This phenomenon has not been observed in control animals. (Figs. 9, 10 and 11.) It may be assumed, although not necessarily proved, that these processes also occur in obstructed lymphatics.

In a more detailed analysis of these experimental studies⁷ several facts were

immediately apparent. Patency can be reestablished in experimental veins even as long as six days after a clinically visible and microscopically demonstrable thrombus is present. Since it is well known that heparin *in vitro* has no effect on fibrin, it seems difficult to explain the dissolution of clots up to and including the sixth day after thrombus formation. A critical review of the physical changes resulting in clot formation may afford a possible explanation of our results. The classical early red cell clot consists of red cells enmeshed in an interlacing fibrin network. After varying periods of time, organization occurs within the clot wherein the red cells and fibrin are replaced by young fibrous connective tissue.

In the light of recent work on the functional pathology of experimental frostbite^{12,13} and on the blood flow in malaria and in traumatic shock,²⁵ it may be inferred that the natural history of the classical clot as generally described is not complete. In the presence of injury or infectious disease, Knisely and his co-workers have observed that red cells become "sticky" and adhere to one another; at first, in small clumps which soon become progressively



FIG. 3. Normal jugular vein of a rabbit.



FIG. 4. Photomicrograph of normal jugular vein of a rabbit, all coats intact; $\times 43$.

larger so that blood flow rapidly slows down and the blood itself appears as a thick mucky sludge, similar to the sludge phenomenon in experimental frostbite. The mechanism whereby the red cells become sticky is mediated through the formation of a thick, glassy, cottony precipitate whose appearance and consistency suggests that it might be fibrin or a fibrin-like material. It thus follows that the earliest stage of clot formation, as portrayed in our experimental investigation, may well be represented by a large mass of red cells agglutinated to one another and not as yet exhibiting the usual interlacing fibrin network. In the progressive growth of a clot sludge formation is ever present, both as the propagating tail and as part of the unorganized body of the clot. It is significant that in every instance when pure sludge formation was noted microscopically, despite clinically palpable clot formation, the clot disappeared completely under heparin therapy.

The extent and apparently the speed of recanalization of experimental thrombi is

enhanced by the use of heparin. When the vein is so grossly occluded as to preclude the resumption of clinical patency, recanalization is still greater in degree and extent under heparin therapy. In the presence of occluded veins which cause definite obstruction to circulation, the opening of adjacent collateral venous channels is so extensive in the presence of heparin that the combined cross sectional area of the collateral system appears as great, if not greater than that of the original veins. Any attempt to explain the apparent dissolution of the frank fibrin clot and the rapid recanalization of the late clot under heparin influence must necessarily be speculative. Studies are in progress in an effort to clarify these moot points. Conceivably, a contributing factor in stimulating reparative processes of the mature fibrin clot, such as organization and recanalization, is the demonstrable effectiveness of heparin in enhancing and maintaining an elaborate collateral circulation. It is generally conceded that the phenomenon of recanalization



FIG. 5. Non-heparinized control; jugular veins of a rabbit six days after ligation and hampering; visible and palpable clots have been induced.

FIG. 6. Photomicrograph of jugular vein (Fig. 5) with all coats intact. There is no classic evidence of clot, the blood being present as particulate masses with a minimum of fibrin (sludge); $\times 30$.

is to a large extent predicated on physical factors. It is evident that the larger column of fluid blood, resulting from heparinization, pounding against small, recanalizing channels may well be responsible for accelerating and augmenting organization and recanalization.

Treatment. Although methods of treatment of thrombophlebitis and/or phlebotrombosis are legion, two major thoughts have dominated the clinical scene during the past five years, namely, vein ligation and anticoagulation therapy.

Surgical Interruption of Veins. While our contrary views on the matter of vein ligation have been set forth elsewhere³ the literature abounds in articles advocating this form of therapy. The surgical approach to the problem of thromboembolism was initiated in America by Homans¹⁷ and later elaborated by Welch and Faxon,³¹ Fine,³² Allen and his associates,³³ deTakats³⁴ and others.

The knowledge that the majority of such emboli stem from the veins of the lower extremities led these investigators to divide the suspected vein, after preliminary thrombectomy, on the faintest suspicion of phlebotrombosis. Indications for vein ligation have been based for the most part on clinical signs, whether or not corroborated by positive phlebograms.^{21, 35}

In the few years during which unilateral superficial femoral vein ligation has been practiced, it has become apparent that fatal pulmonary emboli may derive from an unsuspected thrombotic process on the contralateral side so that bilateral superficial vein interruption has now become common practice. Even this procedure does not offer absolute protection against embolization. Allen, Linton and Donaldson report six deaths due to emboli subsequent to femoral vein ligation in a series of 1,300 patients.³⁶ There are, furthermore, known fatalities in

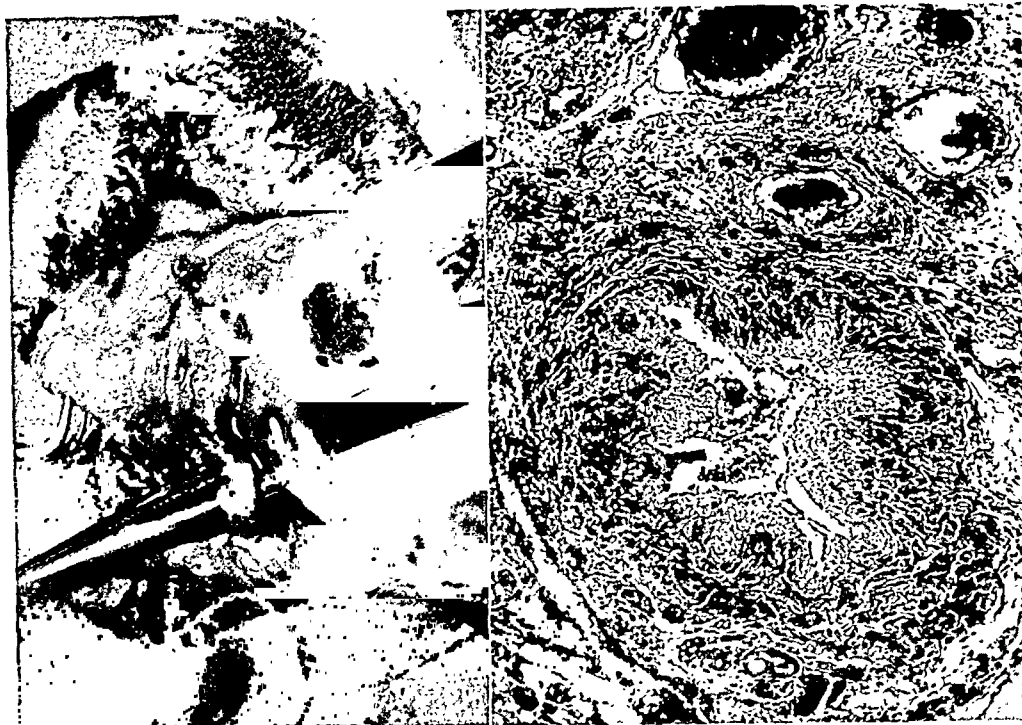


FIG. 7. Jugular veins of a rabbit six days after ligation and hammering, with fourteen days of heparinization superadded. The walls are thickened but no gross evidence of thrombosis is apparent. Compare with Figures 3 and 5.

FIG. 8. Photomicrograph of jugular vein (Fig. 7) with all coats intact; no evidence of clot or fibrin; note beginning collateralization. Compare with Figure 6.

which the offending embolus originated from the profunda femoris vein proximal to the site of ligation of the superficial femoral vein. This has prompted Linton²¹ to divide the common femoral vein. The resultant edema from this procedure has admittedly been troublesome and has been observed to persist for a year or two or longer. Since embolization from the profunda femoris may occur, Homans³⁷ has been impelled to advocate common iliac and even inferior vena cava ligation. However, Homans reports that technical difficulties militate against thrombectomy, particularly in a phlebothrombosis of long standing, so that ligation must of necessity be carried out in continuity, even if a clot is present proximal to the ligature. Obviously embolization from the proximal thrombus is not beyond the realm of possibility.

It must be stated that, although the majority of emboli derive from the peripheral veins, the initiating site may at times be the pelvic veins for which surgical intervention, if it is to be effective, must perforce be a formidable procedure. Finally, in those patients with long standing thrombophlebitis, phlegmasia alba dolens, in which multiple infarcts have occurred, any surgical intervention short of vena cava ligation offers little prospect of cure.

It thus appears that the pendulum of surgical therapy has reached the peak of its swing and the relatively innocuous procedures of a few years ago are being supplanted by operations of considerable magnitude. In view of the failure to achieve a complete thrombectomy consistently in patients in whom adherent clot was found far proximal to the phlebotomy or because of the hazard of subsequent postoperative

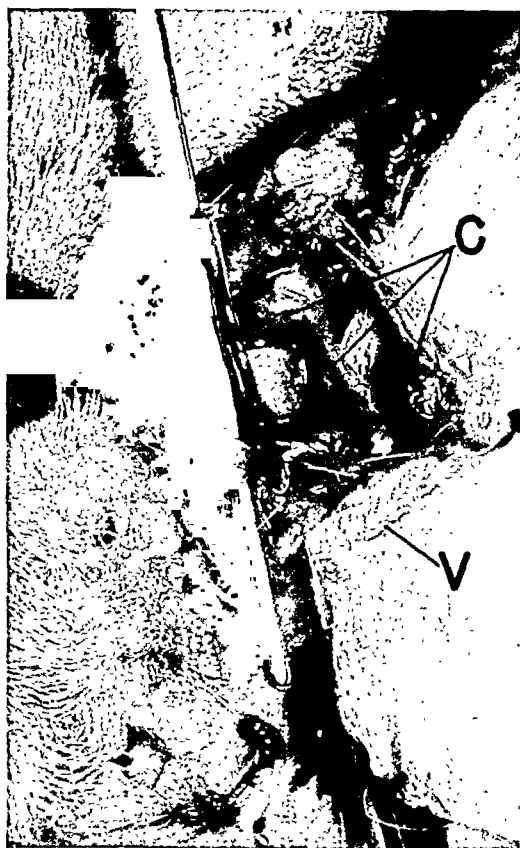


FIG. 9. Jugular vein of a rabbit fourteen days after ligation and hammering with fourteen days of heparinization superadded. Minimal, if any, blood flow through the traumatized vessel (v). Note the rich, dilated, extensive compensatory collaterals (c). Compare with control, non-heparinized veins in Figure 11.

embolizations, whether or not they are sublethal, Bancroft⁹ has advocated the post-operative use of heparin. Indeed, Allen²¹ reports that for patients with multiple infarcts heparinization has been used with definite benefit.

Although saving of life is the prime consideration of surgery, the resultant edema is most troublesome to the patient. Operative procedures which interrupt not only venous but also lymphatic channels contribute considerably to this edema. While conservative treatment without heparin, consisting in the main only of bed rest and sedation, may occasion considerable edema in those who survive, the supplemental use



FIG. 10. Collateral vessel fourteen days after ligation and hammering of jugular vein with fourteen days of heparinization superadded. All the characteristics of a normal vein are present; $\times 27$.

of heparin/Pitkin menstruum results in minimal residual edema, certainly far less than that observed following operative intervention.

It appears that the surgical approach, while efficacious in the majority of cases, has its limitations. In view of the complications of the surgical approach in the treatment of thromboembolic disease, it is apparent that the anticoagulants assume prime importance.

Anticoagulation Therapy. Anticoagulation therapy deals with the abnormal physiology of blood and lymph in the body. Of the anticoagulants, dicumarol and heparin have been the most widely used.

Recourse to dicumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty in planning dosage

schedules and more important, because of its dangerous complications.³⁸⁻⁴² There is great variability in the response to dicumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of dicumarol is slow, from forty-eight to seventy-two hours being required before its therapeutic effectiveness is achieved. This delay in action is due to the fact that dicumarol's anticoagulation action is a reflection of its attack on the liver, inhibiting the formation of prothrombin.

Due to delay in action and the variability of the patient's response the drug is not always useful in the early critical stages of coronary thrombosis, in arterial thromboembolism generally and in arteriotomy or major pulmonary embolism when prompt anticoagulation effect is imperative. The delayed action and prolongation of effect after cessation of therapy are disadvantages during or shortly after operative procedures as well as in patients with anticipated, threatened or actual hemorrhage. Instances have been observed in which embolism, thromboses or progression of existing venous thromboses have occurred despite low blood prothrombins induced by dicumarol.⁴⁰ Patients receiving dicumarol require daily prothrombin determinations. Dicumarol should not be employed unless there are proper laboratory facilities for prothrombin determinations by acceptable technics. The latter are time consuming and relatively expensive.

In the presence of liver disease the use of dicumarol is contraindicated. It has been attended by irreversible hemorrhage and death.⁴¹ Transfusions of fresh blood alone do not arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, in turn, reinduce thrombosis.⁴²

In summary then, the delayed action,



FIG. 11. Non-heparinized control; jugular veins of a rabbit fourteen days after ligation and hammering. The veins are thickened and fibrotic. Note the absence of compensatory collaterals. Compare with Figure 9.

potential hazards, the unpredictable treatment failures and the requisite complicated but indispensable laboratory procedures militate against dicumarol as the anticoagulant of choice.

The properties of heparin which render it uniquely applicable in thromboembolic disease have already been enumerated. Until recently the routine use of heparin has been limited by the expense, the huge amount of drug required in the individual case and the cumbersome method of administration, which requires a continuous venoclysis or repeated daily intravenous dosage. The restriction of motion of the patient, the almost absolute certainty that superficial angitis would eventually occur at the site of injection and the haphazard control of the clotting time rendered heparin therapy useless unless constant supervision was available.

In an attempt to achieve prolonged absorption of heparin, pellet and capsule

implantation in experimental animals was attempted. Erratic, unpredictable effects were observed. However, a slower and more uniform distribution of heparin was obtained by incorporation of the drug in the Pitkin menstruum developed to regulate

TABLE I
HEPARIN/PITKIN MENSTRUUM FORMULAS

	With Vasoconstrictors		Without Vasoconstrictors	
Heparin, sodium salt, mg	3000	2000	3000	2000
Epinephrine hydrochloride, mg	10	10	0	0
Ephedrine sulfate, mg	250	250	0	0
Chlorobutanol, mg	05	05	05	05
Eucupin dihydrochloride, mg	10	10	10	10
Pitkin menstruum, cc	30	20	30	20

the rate of release of water-soluble drugs injected intramuscularly or subcutaneously.^{1,2}

The ingredients of the Pitkin menstruum are gelatin 15 to 30 per cent, dextrose 5 to 12 per cent, glacial acetic acid 0.5 per cent and sufficient distilled water to make 100 per cent. The rate of liberation of the contained heparin is inversely proportional to the viscosity of the menstruum; the optimum percentage of gelatin and dextrose were found to be 18 and 8 per cent, respectively, for the preparation containing heparin.

Heparin/Pitkin Menstruum. The ampuls* for clinical use (Table I) are as follows:

Heparin/Pitkin menstruum (v.c.)

Ampuls, 2 cc.—each ampul containing 200 mg. heparin sodium salt with vasoconstrictors.

Ampuls, 3 cc.—each ampul containing 300 mg. heparin sodium salt with vasoconstrictors.

Heparin/Pitkin menstruum (plain)

Ampuls, 2 cc.—each ampul containing 200 mg. heparin sodium salt; no vasoconstrictors.

Ampuls, 3 cc.—each ampul containing 300 mg. heparin sodium salt; no vasoconstrictors.

Dosage Plan. In general, body weight and individual reactivity dictate the amount of heparin/Pitkin menstruum to be used in a

* Prepared and distributed by William R. Warner & Co., Inc., New York.

given case. For the initial injection, body weight may be used as a guide. Patients weighing up to approximately 150 pounds (67.8 Kg.) should be given an initial dose of 300 mg. of heparin sodium salt, patients over this weight should be given an initial dose of 400 mg. Subsequently, the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of nine to fifteen minutes (Lee-White modification of Howell's method), a coagulation time of thirty to sixty minutes is considered an adequate "heparin effect." In actual practice it will be found that a conventional dose of 300 mg. of heparin will suffice for about 90 per cent of subjects who are normal reactors. The remaining 10 per cent are either hyper- or hyporeactors requiring 200 or 400 mg. dosages, respectively.

Method of Administration. (1) Warm the ampul gently either by holding it under running, hot tap water or immersing it in a container of hot tap water until the contents become fluid; (2) shake thoroughly to disperse any precipitated material; (3) draw the contents of the ampul into a dry, sterile 5 or 10 cc. syringe, using a sterile needle, gauge 18 (2 inch length). After the contents have been drawn up, the 18-gauge needle should be replaced by a 20-gauge needle for the actual injection; (4) inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thighs alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injection area; (5) be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm and (6) do not apply either heat or cold to areas of deposition unless for

purposes of accelerating or retarding release of the drug.

Clinical Use. In the average patient use the entire contents of one 3 cc. ampul containing 300 mg. of heparin sodium salt. This dose should be sufficient to keep the patient "heparinized" for approximately two days. (Fig. 12.) Therefore, administer the contents of one 3 cc. ampul every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during the period of heparinization, administer the contents of one 3 cc. ampul immediately following the transfusion, irrespective of when or how many previous deposits have been given.

Method of Following the Patient's Clinical Course. The effect of heparin is judged by and based on determination of the blood coagulation time, which should be estimated daily throughout the period of heparinization. The capillary tube method is inaccurate and should not be used. The Lee-White modification of Howell's method for determination of blood coagulation time is recommended. The technic of performing and estimating coagulation time is as follows:

- (1) Place four chemically clean, dry 75 × 10 mm. test tubes in a rack. (2) With a sterile, dry syringe and needle withdraw about 2 cc. of venous blood from the subject. The test is timed from the moment the blood is first observed in the syringe. Remove the needle from the syringe. (3) Gently distribute approximately 0.5 cc. of blood into each test tube. Discard the last air-containing fraction. (4) All glassware, syringes and needles must be absolutely dry. Moisture, alcohol, etc., invalidate the determination. (5) The vein must be negotiated cleanly. If difficulty is encountered, it is best to use a fresh needle and syringe. Even a small amount of tissue juice aspirated into the syringe will give a false result. (6) Once the blood is placed in the test tubes they must be

disturbed as little as possible while observing for the end point. It will be noticed that well heparinized blood will sediment very rapidly. The tubes should not be shaken after sedimentation of the blood. Look for clotting in the red cell layer as well as in the plasma

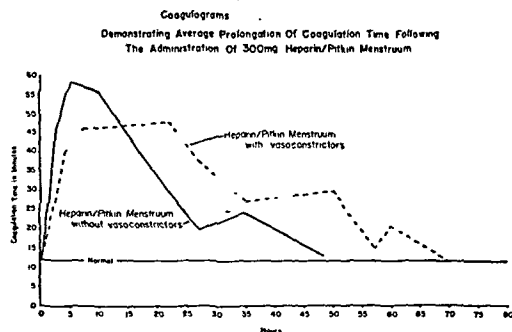


FIG. 12. Coagulograms demonstrating average prolongation of coagulation times following the administration of 300 mg. heparin/Pitkin menstruum.

layer by gently tilting the tubes. In unclotted blood the red cell layer will flow as the tube is angled. (7) First, gently tilt one tube and note the flow of the red cell layer. If the flow is rapid discard the tube and wait about five minutes before the second tube is angled. In this way the end point may be approximated and then finally accurately determined from the third or fourth tube. Once any of the tubes are disturbed they should be discarded, and (8) the patient's coagulation time should be determined before heparinization for control purposes, after which the coagulation time should be estimated daily (twenty-four hours after the heparin injection and immediately before the next injection.

REACTIONS, COMPLICATIONS IN THE USE OF HEPARIN/PITKIN MENSTRUUM

- (1) The local pain, swelling and tenderness of the earlier preparations is ascribable to the precipitate which was found to be due to a combination of heparin and eucupin. The pain factor induced by this precipitate was at times excessive but could be con-

trolled by adequate sedation. This objection to the preparation, the pain factor so disturbing to the patient, has now been controlled by careful buffering so that the pH of the gel is more physiologically acceptable and the tendency to precipitation noted in the original ampuls is overcome. Other side effects of the heparin Pitkin menstruum preparations are trivial.^{3,5,10} On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization in a patient with postpartum thrombophlebitis. The patient made an uneventful recovery.

(2) Following the administration of a dose of 200 or 300 mg. of heparin sodium salt combined with vasoconstrictor drugs, the patient will occasionally complain of palpitation and nervousness. These reactions require no treatment and disappear within a short time.

(3) Digitalis is said to inhibit the anticoagulant action of heparin. If possible avoid the use of this drug during the period of heparinization.

(4) If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag applied to the site of deposit or a tourniquet above it will suspend or slow up the absorption of the drug. In our experience the use of protamine for abrupt interruption of heparinization has not been necessary.

(5) In hypertensive patients or those with myocardial disease it is preferable although not mandatory to use heparin without vasoconstrictor drugs in order to avoid the transitory subjective vasoconstrictor effects.

Suggestions for Treatment. (1) In patients with thrombophlebitis it is advisable to inject the heparin into the thigh which is normal. Avoid using the affected thigh for

deposition of heparin until the swelling has partially receded. (2) For hyper-reactors employ the 2 cc. ampul which contains 200 mg. of heparin sodium salt. For hyporeactors administer 400 mg. This is accomplished by combining two cc. ampuls each containing 200 mg. of heparin sodium salt. When vasoconstrictors are indicated use only one ampul with vasoconstrictors in the combination, inasmuch as the amount of vasoconstrictor drugs contained in the one ampul will suffice for the entire dose of heparin. (3) As a general rule, for effective heparinization the blood coagulation time should be not less than three times the control coagulation time, i.e., thirty to forty-five minutes as contrasted with a control time of nine to fifteen minutes.

CLINICAL DIAGNOSIS

For optimum results heparin therapy should be inaugurated as early as possible. The advantages of preventing spread of thrombosis before it may give rise to pulmonary embolism or serious local damage are obvious and have been stressed repeatedly in the literature.⁴³ Admittedly, thromboembolism may be a treacherous and unpredictable condition; at times it occurs catastrophically and without warning. Nevertheless, if one is alert for slight premonitory signs, these will be discovered more often than has been supposed. One such diagnostic sign, described by Allen,²¹ is an inexplicable rise in the pulse, temperature and respiration at the same reading or observation. When after operation these have shown the normal downward course, any fresh rise, however small, after the fourth or fifth day must always evoke suspicion. This applies also to the parturient and to patients with fractures. Another sign sometimes observed is an unaccountable feeling of disquietude and restlessness which affects the patient. He may state, perhaps not until questioned, that he was

kept awake during the night by a faint ache and a feeling of cramp in one of the calves, so-called "charley horse," a symptom which may already have disappeared. Complaint of even a slight stitch or pain in the chest must arouse strong suspicion of pulmonary infarction which is confirmed if the patient develops an irritative cough or expectorates blood-streaked sputum. It may be assumed that the majority of so-called "lung complications" observed postoperatively or postpartum, as well as in aged people confined to bed for reasons other than general debility, are due to pulmonary infarcts secondary to thrombosis somewhere in the peripheral parts of the body.

If any of these general signs are noted, a detailed physical examination must be made to elicit the cause. Examination consists of palpation of the groins, inner aspect of the thighs, popliteal spaces, the calves and the veins of the feet for swelling and tender areas. Conspicuous signs need not necessarily be present. In early cases one may note only slight swelling of the lower leg, an increased glossiness and tension of the skin, a faintly cyanotic discoloration in comparison with the other leg and prominence of the superficial veins of one leg as compared with the other. All these signs need not necessarily be present but if one or more of them is observed the probability of an incipient thrombosis is considerably increased.

The most important sign is direct tenderness in the calf, discovered by pressure with the palpating fingers. Such tenderness will be more significant if none is elicited when the muscles of the same level are compressed from side to side. An increase in the consistency of the muscular part of the calf is another customary feature of thrombosis. Finally, the foot is brought into dorsal flexion and if pain is induced (Homans' sign) it is very suggestive of deep venous thrombosis.

Phlebography. The clinical importance

of phlebography of the lower extremities is still unsettled. It seemed to us that the latter could be more clearly defined as an aid to the evaluation of the procedure. In a study by Epstein, Wasch and Loewe,⁴⁴ apparently normal individuals were subjected to phlebography of the lower extremities, as a result of which the following conclusions seemed warranted. Within its limitations phlebography may provide information as to the patency of the superficial and deep venous circulation. The normal variations which may be observed in phlebograms of the leg make it hazardous to venture a diagnosis in the absence of very striking changes. There is a marked variation in the appearance of the deep leg veins which makes it extremely difficult to reach any trustworthy conclusion as to the presence of intrinsic thrombotic changes in those areas. The appearance of the popliteal and femoral vein is more consistent but here, too, normal variations occur which may confuse the unwary into venturing a diagnosis of thrombotic changes. Because of the difficulty of establishing the normal standard we have abandoned the routine clinical use of phlebography.

ANALYSIS OF RESULTS AND CLINICAL OBSERVATIONS

The clinical deportment of heparin/Pitkin menstruum has been observed in 251 patients representing all forms of venous thromboembolic disease. (Table II.) Some of the categories have afforded more cases than others but, on the whole, there are a sufficient number of cases for purposes of observing and evaluating the effects of heparin/Pitkin menstruum in thromboembolic disease. The results have been most gratifying, being signally successful in thrombophlebitis irrespective of etiology.

The final judgment in any treatment program for thromboembolic disease is predicated on the statistics with respect to pul-

monary embolization. It is noteworthy that of the 251 patients, ninety-five had from one to six pulmonary embolizations prior to initiating subcutaneous heparin therapy. There were five fatalities in this series of 251 patients (1.9 per cent). Four of the fatalities

TABLE II
HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 251
CONSECUTIVE PATIENTS WITH VENOUS THROMBOEMBOLIC
DISEASE

Classification	No. of Patients	No. of Patients with Pulmonary Embolization	Deaths Due to Pulmonary Embolization
Post-operative Thrombophlebitis and/or Phlebotrombosis	102	45	3
Thrombophlebitis and/or Phlebo- trombosis, Miscellaneous*	92	38	1
Post-partum Thrombophlebitis	30	7	0
Post-infectious Thrombophlebitis	10	0	0
Post-traumatic Thrombophlebitis	6	5	1
Migrating Thrombophlebitis	9	0	0
Totals	251	95	5 (1.9)†

* Occurring without ascertainable exciting cause (thrombophlebitis), or as a complication of carcinoma, varicose veins, etc.

† 4 of the 5 treatment failures occurred before the optimum treatment program was established.

came early in our experience and served as an object lesson for standardizing and formulating our present program of therapy and dosage schedules.

The fifth treatment failure occurred in a sixty-three year old obese, white woman who had, at the outset, an obscure clinical syndrome which ultimately proved to be bilateral massive thrombophlebitis with repeated extensive pulmonary embolic episodes. The clinical diagnosis was at no time characteristic and even after thrombotic involvement of peripheral veins was evident, it was believed that the clinical picture was secondary to an underlying malignancy. Heparin/Pitkin menstuum therapy was inaugurated more than three weeks after the known onset of the condition. A standard dosage schedule was administered, the patient receiving 300 mg. of heparin/Pitkin menstuum subcutaneously every other day for five injections with seemingly satisfactory anticoagulation responses. Despite this the patient went into deep shock as a result of massive pulmonary embolus. At necropsy the deep veins of both lower extremities were found to be completely occluded, with massive thromboses extending up to and

involving both femorals, iliacs, the inferior vena cava, ovarian veins and renal veins. The extent of the thrombotic lesion, which was never suspected clinically, evidently made the patient refractory to the average doses of heparin. Our experience leads us to believe that there is a parallelism between thrombus mass and heparin requirements. Had the extent of the lesion been recognized and the dosages intensified, further thrombus formation might perhaps have been prevented. It seems hardly likely that the patient would have survived high vena cava ligation, nor is it possible to assume that further embolization would have been obviated. As a result of the experience in this patient the following program has been formulated. Once the diagnosis of thrombophlebitis or venous thromboembolism has been entertained in an individual who has been ill for some time, it must be assumed that the condition has, from the very outset, been one of intravascular thrombosis and a greatly intensified dosage schedule must be instituted. Such a dosage schedule might well be 400 to 500 mg. every other day, or even daily, in order to maintain coagulation times between one and two hours. This compares with a coagulogram of thirty to sixty minutes obtained with conventional dosages of 300 mg. every other day, which is adequate for the average patient. It may well be that patients with massive, widespread thromboses can be salvaged only in this manner, if at all. The importance of early diagnosis in order to obtain optimum results cannot be overemphasized.

In contrast to these treatment failures, mention may be made of seven patients with multiple pulmonary emboli despite vein ligation, with complete recovery following use of the subcutaneous heparin preparation.

Particularly significant and informative are the twenty-two patients who were successfully treated with heparin in the Pitkin

menstruum following single or multiple massive pulmonary embolizations without any manifestation of peripheral vein involvement; these patients could not conceivably be subjects for proximal vein ligation. Finally, it is worthy of comment that in seven patients subcutaneous heparin was successfully employed following failure with dicumarol.

In uncomplicated phlebothrombosis, heparinization need be continued only for seven to ten days, while cases complicated by pulmonary infarction, either single or multiple, require an additional seven to ten days of heparinization. The full heparin effect must be present when the patient is first allowed out of bed and continued until the patient is fully ambulatory. This conservative span of treatment is postulated not only on the basis of clinical experience but also as the result of experimental work indicating the time needed for restoration of the vascular stream and the importance of giving sufficient treatment to allow and promote collateralization and development of the tributary vein system.

It is evident from a critical review of our series of patients that our extensive trial of subcutaneous heparin in the Pitkin menstruum has given good results. Sulfonamides and penicillin may be used in conjunction with heparin but heparin alone in clinically established thrombophlebitis, irrespective of etiology, consistently gives good if not dramatic results. These include diminution of temperature, pain and swelling, which often become manifest within a few hours after initiation of therapy. This improvement is predicated on limitation in the progress of the formed thrombus, while the original inflammation expends itself and the thrombus either resolves or becomes organized. Since there is no further actual propagation of thrombus, there is a rapid and marked diminution in vasospasm. Morbidity is lessened and convalescence accelerated.

Coincident with the institution of heparin therapy the liberal use of papaverine is recommended, 1 to 3 grains every four hours intramuscularly or even intravenously and, later, maintenance dosages by mouth. Smoking is strictly prohibited. Paravertebral block, although used extensively in arterial occlusions, is not used by us in thrombophlebitis as a routine measure since we have found that venous spasm disappears promptly following administration of subcutaneous heparin.

As has been described earlier the general systemic anticoagulation effect of heparin seems to us to be a more rational therapeutic weapon than local vein ligation, especially since the precipitating cause of thrombosis is not yet known and the initiating site of thrombosis can be ascertained in many cases only by vague and indeterminate clinical signs. The ready availability of immediate, adequate and rational conservative treatment without moving the patient has caused vein ligation to be supplanted in our clinic by subcutaneous heparin therapy.

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF THROMBOEMBOLIC DISEASE COMPLICATING THE PUE- PERIUM AND GYNECOLOGIC SURGERY

Of the 251 patients with venous thromboembolic disease (Table II) receiving heparin/Pitkin menstruum, fifty-three (Table III) were obstetric or gynecologic patients. Thirty-four of these fifty-three patients were obstetric and nineteen presented gynecologic problems. One of the thirty-four parturients received the treatment for phlegmasia alba dolens which developed forty-eight hours prior to the onset of labor. In the latter patient the therapy was interrupted during actual labor and was begun again in the postpartum period. Instructions to interrupt heparinization at the very onset

of labor were not carried out until several hours after delivery. Significantly in this case there was somewhat less than the anticipated amount of immediate post-delivery bleeding, despite the fact that the patient was actively heparinized at the time of de-

TABLE III

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 53 PATIENTS WITH THROMBOEMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY

Classification	No. of Patients	No. of Patients with Pulmonary Embolization	Deaths Due to Pulmonary Embolization
Pre-partum Thrombophlebitis	1	0	0
Post-partum Thrombophlebitis	29	7	0
Post-operative Thrombophlebitis and/or Phlebothrombosis			
Cesarean Section	4	1	1
Hysterectomy	15	9	0
Vaginal Plastic	4	1	0
Total	53	18	1 (2.3%)

livery. Of the remaining thirty-three parturients, twenty-nine were delivered vaginally and four by cesarean section. Eight of the parturients embolized prior to therapy, in two cases despite femoral vein ligation. Two patients were dicumarol failures prior to inaugurating subcutaneous heparin/Pitkin menstuum therapy. Manifestations of thromboembolism were present in nineteen postoperative gynecologic patients; fifteen following abdominal hysterectomy and four following vaginal plastic procedures. Ten in the group had one or more pulmonary emboli prior to heparin therapy and four patients had emboli despite vein ligations.

The heparin treatment program was that adopted for venous thromboembolism. The span of treatment for uncomplicated thrombophlebitis and/or phlebothrombosis was ten days to two weeks. For patients with pulmonary embolization an additional week or two of therapy was required depending upon the extent of pulmonary infarction. In any event the full heparin effect was present when the patient was first allowed out of bed.

Most informative are the statistics with respect to the patients who had pulmonary embolization. There were eighteen patients in this group with one fatality, representing

1.8 per cent of the entire series of fifty-three patients and 5.5 per cent of the eighteen patients who had suffered from one or more episodes of pulmonary embolization.

The treatment failure, as previously reported, followed sequential femoral vein ligation for recurrent pulmonary embolization incidental to phlebothrombosis following operation for premature separation of the placenta. Subcutaneous heparin was discontinued prematurely two days after the initial left femoral ligation, because the pulmonary findings were attributed to virus pneumonia which was prevalent at the time. The right femoral vein was ligated about ten days after the left femoral vein ligation. Lethal massive pulmonary embolization ensued on the third day following the right femoral vein ligation. Necropsy disclosed old, adherent thrombi in the left iliac and left hypogastric veins which were probably the source of the emboli found occluding the right pulmonary artery and main branch of the left lower lobe.

This fatality, the only one in this group of gynecologic and obstetric patients, must be catalogued as a treatment failure for combined thrombectomy, vein ligation and supplemental subcutaneous heparin therapy, although the latter was suspended after much too short a span of treatment.

One of the obstetric patients suffered a hematoma at the site of one of the injections which did not interfere with the progress of the treatment program, the patient making an uneventful recovery. In this patient, as in all the other patients treated in the early stages of the disease, the hospital stay was definitely curtailed and the disfigurement eliminated or significantly reduced.

While the addition of antibiotics and/or sulfonamides to the treatment program is not discouraged, these are not necessary in the management of the usual type of thromboembolism encountered in obstetric and gynecologic practice. However, should there

be any identifiable infective etiologic condition, an antibiotic and/or chemotherapeutic program should be pursued intensively according to the nature of the infective organism. The mere presence of a febrile reaction does not connote bacterial invasion and may well be attributable to the presence of intravascular thrombosis, particularly when the blood clot engages the vessel wall and precipitates an inflammatory intimal reaction.

The results in this series are satisfactory as judged by effective control of pulmonary embolization, marked amelioration of pain and discomfort, rapid recession of edema, reduction in morbidity, acceleration in convalescence and virtual absence of residual edema particularly when patients are treated without delay.

PROPHYLAXIS

The problem of prophylaxis in the field of thromboembolism has engaged our attention as it pertains to the use of subcutaneous heparin/Pitkin menstruum.

Despite early ambulation in the postoperative and postpartum patient, there is an irreducible occurrence of venous thromboembolism.^{36,45} The widespread general use of anticoagulation therapy in the prospective surgical and obstetric patient, while ideal, is not practical or feasible at present. As a result we have expended a great deal of time and effort in an endeavor to detect the potential clotter, the thrombophilic. A straw in the wind is the report by Morrison, Richter and Loewe on blood platelet clustering.⁴⁶ The report deals with the method and interpretation of a proposed clustering test. Clustering and/or increase in numbers of platelets is directly proportional to their coagulability. The most obvious characteristic of the blood platelet is its clustering propensity.^{26,27} A simple routine blood platelet clustering test was devised as a means of establishing the coagulative status of individuals in comparative health and in

disease. In a study of 200 subjects a correlation between this test and thromboembolism was indicated. Its value as a means of detecting the clusterer, the thrombophilic and potential clotter, was suggested. The presumptive thrombophilic and potential clotter, identified by his blood smear, may then conceivably be protected by proper anticoagulation measures during pregnancy and infections, prior to anesthesia and pre- and postoperatively. Clinical and experimental investigation of the rôle of blood platelet clustering in health and disease is being pursued.

While the use of anticoagulants preoperatively is not generally advocated at present, its prepartum use has been suggested in recent reports.^{47,48} Our own related experience with heparin/Pitkin menstruum in the obstetric wards may well suggest its ultimate adoption as a prophylactic prepartum measure.

A rich field for prophylaxis is in the management of patients with severe coronary artery disease and coronary artery incompetency who are extremely susceptible subjects for coronary artery thrombosis. This was originally suggested by the ease with which heparinization was continued and accomplished for long periods of time in ambulatory patients who were up and about following severe intravascular thromboses. We consistently encountered patients who required doses of 300 to 400 mg. of heparin in the Pitkin menstruum every other day in order to achieve adequate coagulograms during the active phases of the disease. These same patients, when there was no longer any clinical or other evidence of the persistence of thrombosis, could then be maintained in a heparinized state on as little as 100 mg. of heparin in the Pitkin menstruum deposited every second to seventh day or longer. This spacing permitted the patients to be treated as ambulatory subjects without inconvenience. As already

indicated there is apparently a direct relationship between the mass and extent of thrombosis and the degree of response to heparin. As the clots disappear the individual becomes less resistant and more responsive to the anticoagulant.

The results of our prophylactic management of ambulatory patients with thrombophilia, recurrent thrombophlebitis, potential coronary artery thrombosis, peripheral vascular disease with menace of complicating thrombosis, or the cardiovalvular patient with or without auricular fibrillation who is suspected of having thrombi in the chambers of the heart or in peripheral veins, have been sufficiently gratifying to justify continuation of the project.

The prophylactic use of heparin/Pitkin menstruum in blood vessel surgery has been recommended by Blakemore and Lord⁴⁹ and its use in the prevention of gangrene following frostbite is suggested by the experimental work done in this field.^{12,13}

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF ARTERIAL THROMBOTIC DISEASE

Results in the conservative treatment of venous thromboembolic disease with subcutaneous heparin in the Pitkin menstruum have been so gratifying that it seemed logical to apply this therapy to the management of arterial thrombotic disease. Exploratory studies were done in order to observe the clinical behavior of this preparation in the presence of various types of intra-arterial clotting. The clinical observations were sufficiently promising to justify a preliminary report.⁶

Peripheral Vascular Disease. The various arterial lesions included in this study were intra-arterial emboli, diabetic gangrene, thromboangiitis obliterans and ergotism.

Although the pathogenesis differs in the various thrombotic diseases of the peripheral arteries the common denominator is throm-

bus formation. While recanalization of thrombus may supervene sufficiently to maintain the vascular stream and retain the viability of the affected limb, as a rule loss of tissue with gangrene is the ultimate fate of the untreated case of intra-arterial thrombotic occlusion. Through the use of heparin propagation of thrombus is inhibited and the patency of the affected vessel and uninvolvement of collaterals is maintained. As a result loss of tissue is minimized or completely obviated and recanalization of the affected major vessel is enhanced. Clinical observations thus far have shown satisfactory response in terms of amelioration of pain, restoration of normal color, tone and lividity to the tissues, delineation of any gangrenous process and increase in pulsation of blood vessels in the affected parts. In general, those patients fared best who received the optimum treatment program within a few hours after the occlusive process became evident.

It is advisable to use heparin without vasoconstrictor drugs (Table 1) in thrombotic arterial disease in order not to aggravate the complicating factor of arterial spasm. This may necessitate more frequent administration or a stepped up dosage plan (400 mg. every other day or daily) because of the more rapid depletion of the individual deposit.

Papaverine is used concomitantly in liberal dosages, first by the intramuscular or intravenous route in 1 to 3 gr. dosages and subsequently by mouth in maintenance dosages of 1 to 1½ gr. every four hours. Paravertebral sympathetic block is used when indicated and repeated whenever necessary in the presence of protracted vasospasm. The vasospasm is apparent for the most part during the early stages of the treatment program before heparinization is in full effect. Rarely is sympathetic block necessary following the first or second deposit of heparin/Pitkin menstruum. The

conjoint use of Etamon (tetraethylammonium)* as a means of supplanting sympathetic nerve block is being explored.⁵⁰

Heparin/Pitkin Menstruum in the Treatment of Thrombosis of Cerebral Arteries or of Retinal Vessels. This has been attempted with signal success only in the few patients treated very soon after the thrombosis occurred. A delay of but a few hours results in irreversible damage to brain tissues due to the ischemia and irreversible damage to the receptor mechanism of the eye. In cerebral thrombosis there is the added hazard of distinguishing between cerebral hemorrhage and cerebral thrombosis; when there is any possible equivocation regarding the diagnosis, anticoagulation therapy must, of course, be withheld.

Heparin/Pitkin Menstruum in Coronary Artery Thrombosis. Coronary artery thrombosis offers a very fertile field for anticoagulation therapy. In coronary artery thrombosis there is a triphasic therapeutic attack. First, and most important perhaps, is to prevent propagation of the thrombus from what, in many instances, is merely an occlusive involvement of small twigs of the coronary vessels. In this manner it is hoped to limit the degree of myocardial infarction and consequent myocardial damage. All too often the propagation thrombus is the lethal factor. The second treatment approach is prevention of embolization from mural thrombi secondary to the myocardial infarction. The third phase of the treatment is leveled at the not infrequent thrombotic involvement of deep venous channels resulting from slowing of the vascular stream in the bedridden convalescent patient. The ominous resultant pulmonary embolization may be clinically confusing at times and erroneously attributed to cardiac factors. Dicumarol is admittedly useful only in the second and third phases of therapy⁵¹⁻⁵³ and is not help-

ful, because of its delayed action, in the initial phase of thrombus propagation. Heparin/Pitkin menstruum, because of its prompt action and simplicity of subcutaneous administration, would seem to be the anticoagulant of choice, particularly in the initial and important aspect of coronary thrombosis. The results in a controlled series of patients with acute coronary thrombosis, electrocardiographically confirmed, have thus far been most encouraging. For optimum effects the immediate administration of anticoagulation therapy is essential.

SUMMARY AND CONCLUSIONS

1. The functional pathology of intravascular clotting has been outlined as a basis for evaluating the treatment of thromboembolic disease. The rationale of anticoagulation therapy has been presented.

2. Experimental investigations and clinical observations indicate that heparin plays a vital rôle in arresting the progress of intravascular thrombosis and promotes restoration of the vascular stream. It also enhances collateralization.

3. Over 400 patients with various forms of thromboembolic disease have been treated with heparin/Pitkin menstruum. This series included 251 consecutive patients with venous thromboembolic disease.

4. The treatment of venous thromboembolic disease with subcutaneous heparin in the Pitkin menstruum was attended with lessened morbidity, prompt and rapid clinical improvement and little or no residual edema. The causative factors responsible for the five treatment failures have been analyzed. Treatment failures with other methods have subsequently ended in recovery following the routine administration of the heparin/Pitkin menstruum preparation.

5. Exploratory studies in the field of prophylaxis and in the treatment of various arterial thrombotic disorders, including

* We wish to thank Parke, Davis & Company for generous supplies of this drug.

coronary artery thrombosis and peripheral vascular disease, are sufficiently promising to justify further intensive investigations.

6. As a result of observations of its clinical deportment in over 400 patients with thromboembolic disease, the subcutaneous administration of heparin in the Pitkin menstruum is recommended as a safe, simple, practical and effective method for anticoagulation therapy of intravascular thrombosis.

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Anticoagulant Therapy with Heparin*

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WHILE the etiology of thrombosis and intravascular clotting is still obscure, the presence of this disease can make itself known in one of several mundane or melodramatic ways. The physiologic function of clotting provides for repair in the normal course of events of the vascular system and for the acute emergency of bleeding. It may be life-saving when the vessels are injured, as in external or internal hemorrhage, making this a vital function. However, if the process goes wild or under certain conditions goes into action under adverse circumstances, then instead of being a life-saving measure it may deal a death blow. The action of this function throughout the whole vascular tree, arterial, cardiac, venous and capillary, makes the possible ramifications of the manifestations of clotting a matter of very particular and significant clinical importance.

If the patient with degenerative disease of the vascular bed in the brain has the misfortune to burst a vessel, it is a matter of the greatest importance whether the clotting process can stem the hemorrhage. On the other hand, if in the coronary system a thrombosis occurs, the clot becomes a menace and the prospects for recovery depend on various circumstances which are almost beyond clinical control at the present time. If, in the vessels of the intestinal tract extensive thrombosis occurs, a mesenteric thrombosis, the patient's future is in grave doubt unless surgical interference can eradicate the disease and further thrombosis can be prevented. The benign effect of a local thrombosis in a varix of a varicose venous

tree may have no more importance than the balmy breezes of early spring. However, if a similar process, either by extension or primary effect, involves the important venous trunks in the lower extremity or elsewhere, then a situation is created in which the outcome is most uncertain. Whether the lesion remains localized in this area or will shed an embolus which may be fatal, is purely a matter of accident. Again, in many surgical operations on the vascular tree, especially in the repair of arteries and in the Blalock operation, the appearance of thrombosis may be an advantage under some conditions and under others it may nullify the most careful efforts of the best surgeon and destroy the patient's hopes and prospects for benefit from surgery. The survival of the patient, the survival of the extremities and the reputation of the attending doctor may be at stake.

Because of the possible widespread manifestations of thrombosis and its complication, embolism, and because of the difficulty in defining the area involved and the level to which it has progressed, it would seem exceedingly difficult by surgical means alone to eradicate the threat of the disease. It is impossible to be sure by surgical methods alone that the condition is adequately under control. For that reason, therefore, it is suggested that an anticoagulant which reaches all remote corners of the vascular tree may have advantages under certain conditions. For example, in a patient who has a pulmonary embolism and has survived the initial shock, the prognosis may still be in doubt because of the possibility of the occur-

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ence of another embolism, and also because of possible extension of thrombosis in the pulmonary tree from the embolus already present. It has been well demonstrated by careful dissection of lungs in a case with one large embolus that there can be extension of this embolus to include different and more important branches of the pulmonary tree, until so much was occluded as to cause a fatal issue. This condition is completely outside the range of approach of surgery of the present day. Even though the Trendelenburg operation may remove the original embolus this must be done within a short time. If the embolus has been *in situ* for a few days and progressive thrombosis has occurred, it cannot be removed completely and the patient cannot be protected from extending thrombosis. Under these conditions we have clinical evidence that adequate anticoagulant therapy may prevent the further extension of the disease and allow the condition to heal.

While there are many anticoagulants and many different methods of application, the author's point for discussion in this paper is the administration of heparin by the intravenous drip method or intermittent injection method. While the subcutaneous method has been explored¹ and dicumarol has been administered with satisfaction, nevertheless, he will confine his remarks to the administration of heparin.

The author's experience is based on the administration of heparin experimentally in a great many animals, under various surgical procedures, and on the treatment of patients indicated as follows:

(1) Four hundred postoperative cases in which patients were treated with an anticoagulant with the object of cutting down the incidence of thrombosis and consequently of pulmonary embolism. In this group no patient developed peripheral thrombosis and there were no cases of pulmonary embolism. Our experience ob-

viously includes too few cases to be of much significance except that the treatment was carried out in groups of patients in whom our hospital statistics showed that thrombosis and pulmonary embolism reached the highest recorded figures.

(2) Three hundred eighty-six patients with venous thrombosis in whom treatment by anticoagulants was carried out with the object of preventing pulmonary embolism and as treatment for progressive thrombosis in the venous tree with the hope of relieving symptoms and diminishing the ill effects which are so evident following venous thrombosis, such as persistent edema, varicose veins, ulceration, etc. All these patients had typical symptoms and signs of venous thrombosis before treatment was started.

The results of treatment were satisfactory in that none of the patients had pulmonary embolism; moreover, the late effects of the thrombosis were less severe than in a control group. There was less persisting edema, fewer ulcers in a nine-year period and fewer varicose veins during this time.

(3) One hundred seventy-two patients with pulmonary embolism were treated with anticoagulants. The patients were not selected and obviously were those that had survived the first embolism. In many of these the patients were in extremis at the beginning of treatment. Fifty-two presented a state which is very familiar; the patient in alarming shock, with no palpable pulse at the wrist, bordering on unconsciousness and with all the serious and dreadful effects of massive pulmonary embolism. From an analysis of histories of the hospital, together with the postmortem findings, it has been demonstrated, as shown in a previous paper,² that one in five of all patients surviving the first pulmonary embolism is apt to succumb to future embolisms or to the effects of propagating thrombosis.

This group of patients with pulmonary embolism which the author is reporting in-

cludes only those over whom he had control during treatment. In these he had information that the treatment was adequate and that the necessary effect on the clotting time or on the prothrombin time was obtained. He saw a fairly large number of similar cases in consultation with other doctors who undertook the treatment of the patients and for that reason these patients were not included in this report. Subsequently, the author has learned of three deaths in this group treated by other doctors. In those in whom he had control of the treatment and knew that adequate effects on the clotting and prothrombin times had been obtained, there were no deaths from embolism in 172 patients. Four of these, following the beginning of treatment, had further embolisms which were obviously of small size because they produced only slight effects upon the patient.

It is very impressive to see the effect on a patient with massive pulmonary embolism, extensive thrombophlebitis or both; the improvement that takes place in a matter of a very few hours is striking, once the effect on clotting time has been obtained. The pulmonary distress with dyspnea, pain, etc., together with the embarrassment of heart action, are diminished progressively in a relatively short time so that within a few hours there is a measurable change and within twenty-four to thirty-six hours the alarming symptoms have largely disappeared. It may take several more days before there is complete relief of all symptoms.

During the course of such treatment it has frequently been observed that there was no obvious swelling or edema of the extremities at the time of the massive embolism. However, during the course of treatment one leg would enlarge and show quite a marked edema, and on some occasions, at the same time or within a few days, the other leg would undergo similar changes. It is the author's impression from a study of the

pathologic conditions that this is no indication of ineffectiveness of treatment by anticoagulants. He believes that at the time of the embolism there obviously was a massive thrombus at some site in the venous tree which was so insecurely attached that it broke off and floated off as an embolus. However, at this stage the inflammatory reaction in the wall of the vein and surrounding tissue had not reached the point where it had produced clinical symptoms. While under treatment by the anticoagulant, which can only prevent the further extension of thrombosis, the remaining thrombi have excited the inflammatory local reaction which has undergone the changes that are necessary for the healing of such a lesion.

To accomplish this effect, in the presence of thrombosis or embolism, it is absolutely essential that the original principles of application of anticoagulants be followed. First, if heparin is administered, it must be carried to the point where the clotting time of the patient is kept at or about fifteen minutes. The intravenous method of administering heparin is carried out as follows:

It may be administered as a continuous drip. The heparin may be added to saline, glucose solution or distilled water. The administration is started usually with two vials, or 20,000 units, or 200 mg. in 1,000 cc. of the solution of saline or whatever is being used. With the needle in a vein this is run in continuously at a rate of about thirty drops a minute. Before starting the intravenous infusion, the clotting time of the patient is taken. The heparin is allowed to run in until there is a measurable increase in the clotting time. The ideal situation is to have the clotting time increased to about fifteen minutes. The clotting time determinations are done every two or three hours until this rise in clotting time is detected. When the clotting time reaches fifteen minutes the rate of infusion is slowed down, probably to about twenty drops a minute, but this rate

must be adjusted according to the effect on the clotting time. When the rate of dropping is determined for the patient clotting times are done about twice a day as a check to see that things are going smoothly. Moreover, if the heparin is given following operation, the requirements as healing takes place change somewhat, so that it is necessary to perform clotting times to follow the requirement of the patient as time goes on.

The second method which we used in surgery on the blood vessels, and particularly following a Blalock or Pott's operation on the great vessels of the heart, is to have a continuous intravenous infusion of saline or other suitable solution running in; then into the rubber tube, adjacent to the needle in the vein, a quantity of heparin is injected every hour and one-half. About one hour following this injection the clotting time is taken and it should be elevated to seven or eight minutes. This, the author believes, is somewhat more safe than the continuous drip method because in the former method the rate of dropping may change and there may be alarming effects on the clotting time if this is not controlled adequately. When, however, the injection is given intermittently there is much less chance of giving an overdosage and the whole situation is under better control.

Because the effect of heparin is so evanescent it is necessary to repeat the injection at short intervals; otherwise, too large a dose must be given, raising the clotting time too high if the effect is expected to last longer than one and one-half to two hours. It is no use whatever to give heparin blindly and not know that the effect is being obtained. Since the dose is variable for the individual, the only safe way to be sure of this effect is to do clotting times at short intervals. The next principle is to give the anticoagulant

until the healing process in the area of existing thrombosis has reached the stage when no further thrombosis will take place. In our experience, the average patient who is able to get out of bed should be kept at rest for three or four days under the treatment. Following this, exercise is encouraged and within six or seven days from the beginning of treatment the patient is urged to be out of bed and exercising actively. When the patient can perform this with some energy, probably on the seventh, eighth or ninth day, the heparin treatment is discontinued. If, however, the patient has some lesion or operation which necessitates staying in bed, the treatment is continued for longer periods, up to three and occasionally four weeks; for example, in such cases as spinal fusion when the patient has not been allowed out of bed. It was demonstrated experimentally that a thrombus placed in a vessel is endothelialized well within this period of time and probably that is the best protection against further extension, provided the patient has otherwise returned to normal.

CONCLUSIONS

Thrombosis and clotting may take place in any area in the vascular tree, making it difficult to be sure of effective control by surgical means alone. The universal effects of anticoagulants throughout the vascular bed suggest their value in controlling and treating this disease.

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Conference on Therapy

The Use of Protein Hydrolysates

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. EPHRAIM SHORR: The protein hydrolysate is an outstanding addition to the list of therapeutic agents in recent years. It has applications in several fields of medicine and surgery, and it is for that reason that we have here today experts in these fields to discuss the various aspects of the subject. The problem of providing adequate energy for patients who are unable to take the requisite amount of food-stuffs by mouth has long been a matter of concern. For many years, parenteral alimentation was confined to the use of glucose and salts, except for the occasional and purely experimental trials of other materials, particularly fat. This was the situation until a few years ago when, as the result of the development of protein hydrolysates, it became possible to provide essential amino acids by the parenteral route. What was expected of the protein hydrolysates? Have these expectations been fulfilled? What are their uses and limitations? These are the points to be explored in the conference this afternoon. The discussion will be opened by Dr. Barr.

DR. DAVID P. BARR: As Dr. Shorr has indicated, one of the long sought goals in nutrition has been a diet which is completely adequate for maintenance and growth and which can be administered parenterally. The need is apparent in the care of all those who cannot take food by mouth or who cannot absorb ingested foodstuffs. Glucose, salts and vitamins have

so long been used by injection that the technics are commonplace, but it was not until 1938 that an adequate mixture of amino acids was first successfully given by intravenous injection in humans. The story of how this came about has considerable interest. Many workers have contributed, but, I think, we owe this development chiefly to the early investigations of Robert F. Osborne and Lafayette B. Mendel at Yale and to the very long and painstaking researches of William C. Rose of the University of Illinois. The observations of Osborne and Mendel were made years ago, from about 1911 to 1914. Starting with the feeding of imperfect proteins, gliadin and zein, they discovered that two amino acids, namely, lysine and tryptophane, were essential to normal growth. Their discovery led to extensive investigations with similar methods and to the demonstration in 1928 by Rose and Cox that histidine was also essential. Shortly thereafter, Rose started research along another line, namely, that of feeding mixtures of the pure amino acids. He found that although amino acids were added to the mixtures in the proportions in which they were thought to exist in the protein, casein, they failed to support growth as well as casein itself. Rose's research led rather rapidly to a number of important discoveries: (1) In addition to the previously recognized amino acids, there was another which he called threonine and which was essential to growth; (2)

besides lysine, tryptophane and histidine, there were, including threonine, seven other amino acids apparently indispensable for growth in rats, a total of ten essential amino acids; (3) rats could grow and remain healthy without any of the other amino acids provided these ten were given; (4) while the naturally occurring amino acids were effective in nutrition, the synthetic optical isomers of some of them were ineffective.

The following ten amino acids were found to be essential in the rat: lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine. It was found that arginine could be formed to some extent in the body but not in sufficient amounts to support normal growth. Amino acids other than these ten can apparently be synthesized in the body or dispensed with even in the growing animal.

One of the problems which complicated Rose's investigations was the fact that many of the essential amino acids were effective in nutrition only in their naturally occurring forms. For instance, he found that dextro-histidine could be converted in the body into the naturally occurring levo-histidine. On the other hand, the levo-lysine could not be converted into the natural dextro-lysine. An immense amount of detailed investigative work was necessary to clarify the situation and to discover which amino acids had to be present in their natural form and which could be converted in the body. Rose presented an account of these researches in an important article in *Physiological Reviews* in 1938. He showed that in the case of the five amino acids, valine, leucine, isoleucine, lysine and threonine, only the naturally occurring forms were utilized in nutrition while their isomers were ineffective.

Still other difficulties were encountered in the use of mixtures of amino acids in

nutrition. A vast amount of work was necessary to determine exactly how much of each amino acid was required to maintain growth in humans. The cost of pure amino acids was so inordinately high that few could afford the luxury of maintaining nutrition by their use. The search for substitutes, for impure mixtures, was started at once and was pursued with great energy.

As you know, three methods have been employed for obtaining impure mixtures of amino acids: (1) alkaline hydrolysis; (2) acid hydrolysis and (3) enzymatic hydrolysis. Each has presented practical difficulties. Alkaline hydrolysis is not practical because the exposure of protein to strong alkali leads to rapid racemization of the amino acids so that unnatural forms result. Acid hydrolysis leads to reactions in the mixture which destroy the essential amino acid, tryptophane. For this reason the few acid hydrolysates which are now coming on the market contain added tryptophane. The enzymatic hydrolysis is slower and less complete and produces polypeptides in addition to amino acids. There is always at least a theoretical danger of immunologically active split products of protein in an enzymatic hydrolysate.

Other practical problems arise in the preparation and administration of mixtures of amino acids. Melanin tends to form in some solutions. If the pH is not correctly adjusted, the amino acids may cause acidosis. The concentration of amino acids in solution must be so adjusted as to permit sufficient dosage without undue hydration of the body. To establish nitrogen equilibrium, dextrose must be included in appropriate amounts with the solution of amino acids.

Chief consideration should perhaps be given to the enzymatic hydrolysate which is now in most common use. Mead Johnson and Company was largely responsible for perfecting this material for parenteral ad-

ministration. As you may know, they hydrolyze the protein, casein, with pig pancreas, the enzymes of which convert both the casein and the proteins of the pancreas into amino acids and, to some extent, into the lesser peptides. The product which they call "Amigen" and which is now available in commerce, contains the essential amino acids in approximately the same percentages found in casein: lysine 5.8, tryptophane 1.0, histidine 2.0, phenylalanine 5.6, leucine 13.5, isoleucine 4.8, threonine 4.5, methionine 3.0, valine 5.0 and arginine 5.5. It is important to know that amigen contains about 12 per cent of nitrogen and that about two-thirds of it is in the form of amino acid nitrogen. In other words, 8 per cent of the amigen is amino acid nitrogen.

To Robert Elman of St. Louis, a surgeon, goes the credit for the demonstration that solutions of acid hydrolysates and of the enzymatic hydrolysate amigen can be given safely by intravenous injection in humans. The amigen is supplied in the form of a powder from which solutions may be made, but it is perhaps more satisfactory to use the solutions prepared by the manufacturer, namely, the "Amigen 5 per cent in 5 per cent dextrose solution," or the "Amigen 10 per cent solution." These are so free of pyrogens and dangerous impurities that they may be given with almost as much safety as solutions of glucose.

A liter of a 10 per cent solution of amigen, containing 100 Gm. of the hydrolysate, supplies 366 calories from amino acids and has only a little less than the caloric value of a similar weight of protein which would supply 410 calories. As in the case of protein, the hydrolysate has to be given with sufficient carbohydrate as an additional source of energy if nitrogen balance is to be attained. A solution containing equal amounts of amigen and glucose is unbalanced. Such a solution, namely, one

containing 100 Gm. of amigen and 100 Gm. of glucose per liter, might be given to a patient with a very marked protein deficiency; but under such circumstances, it would probably be preferable to use plasma rather than the protein hydrolysate. For intravenous feeding over a considerable period of time, it is preferable to use each day 3,000 cc. of a solution containing 150 Gm. of amigen (544 calories) and 300 Gm. of glucose (1,230 calories), making a total of 1,774 calories per day. To this a requisite amount of salts and vitamins should be added. The following formula has been used by Albright and others: 3,000 cc. of fluid containing dextrose 300 Gm., amigen 150 Gm., sodium chloride 12.75 Gm., potassium chloride 2 Gm., vitamin C 50 mg., nicotinamide 75 mg., thiamine 5 mg., riboflavine 5 mg., pyridoxine 5 mg., vitamin K 2 mg. and calcium pantothenate 2 mg. With this as the only source of food, they were able to maintain caloric and nitrogen equilibrium over considerable periods, the quantities appearing to represent a complete feeding for a twenty-four-hour period for a person of average size. The solution is given by a continuous intravenous drip using a standard infusion apparatus. There are several difficulties which include the undesirable limitation in the activity of the patient, the need for constant attention of the doctor and the danger of venous thrombosis from prolonged injection. Intravenous alimentation of this kind must be given at a slow rate and 1,000 cc. of such a mixture should not be introduced in less than two hours. When properly administered, disagreeable reactions are surprisingly few. There may be some loss of appetite, sometimes nausea or vomiting and occasionally flushing. When oral feeding is also used, the intravenous injections should be given after meals to avoid interference with appetite. Although intravenous alimentation is always undesirable, its achieve-

ment in practical form represents a therapeutic triumph.

DR. SHORR: Dr. Glenn of the Department of Surgery will now discuss the protein hydrolysates from the standpoint of the surgical problems.

DR. FRANK GLENN: We may briefly classify surgical patients, from the standpoint of the need for proteins, into three groups, namely, those who are deficient in proteins prior to operation, those who develop the hypoproteinemia during the operation and, finally, those in whom the problem arises in the postoperative period. The first group includes patients who are unable to take food or suffer with a disturbance of the digestive apparatus giving rise to impaired absorption or losses due to other causes. In this group are to be found patients with gastrointestinal ulceration, tumors, regional ileitis and colitis. In patients with severe infection there may be reduced intake of proteins or increased destruction. Patients with hyperthyroidism may develop a protein deficiency as the result of the increased metabolism even though their protein intake be high. Patients with acute surgical conditions due to injury may develop a deficiency because of blood loss and shock. Protein loss may be very high in patients with burns. Before any surgical procedure is embarked upon in a patient with hypoproteinemia, it is of great importance to restore the protein level. The operative procedure itself may give rise to hypoproteinemia, partly as the result of hemorrhage and partly as the result of the anesthesia. The anoxia associated with anesthesia may lead to loss of plasma through increase in the permeability of the capillaries. Also, impaired metabolism of the liver cells may take place and in this way give rise to impairment in the synthesis of serum proteins. After the operation, patients lose nitrogen in excess of that of the normal individual. It is

partly due to the reduced intake of food but the loss is greater than can be accounted for by this factor alone. Fever, vomiting, hemorrhage and surgical drainage all contribute to a loss of protein, but there is a decrease in nitrogen retention in patients, even without these avenues of loss. The decrease may be very considerable and may amount to from 1 to 5 pounds of body weight when they are kept in bed for a period of seven to eight days. The problem represents a wasting of muscle due to inactivity.

The loss of protein in the postoperative period is unfavorable to recovery. The hypoproteinemia affects the postoperative course in several ways: It may give rise to pulmonary edema with the increased tendency to pulmonary infection and pneumonia. It may interfere with the healing of wounds in degrees varying from slight impairment of the maturation of fibroblasts to the more extreme cases showing no tissue reaction and dehiscence of the wound. Lowered resistance to infection probably occurs indirectly through impaired detoxifying action of the liver and impaired production of the globulin fractions of proteins which are related to the immune bodies. It also promotes edema of the gastrointestinal tract following surgical procedures, and, that in turn, interferes with the functioning of stomas and restoration of the continuity in the case of gastric resections. This edema may be sufficient to prevent food from passing through stomas which are mechanically large enough. Likewise, it tends to interfere with the peristaltic action of the gastrointestinal tract.

We should pay special attention to the difficulty of determining the true content of serum proteins in the surgical patient. The protein concentration of the serum is often deceptive in the patient who has been dehydrated by vomiting or diarrhea.

A favorable nitrogen balance is of the

first importance in surgical patients. Hypoproteinemia should not be permitted to exist or develop. In the preoperative period, much may be accomplished by blood transfusions, plasma, intravenous amino acid mixtures such as amigen, and protein hydrolysates given orally. In the anemic patient, it is probably wise to discontinue the use of blood transfusions as soon as the red cell count has been restored to normal. The use of plasma for maintaining a favorable protein balance is expensive. The cost of the protein hydrolysates is more moderate. Many patients can take these by mouth if they are properly prepared. If the oral route is not feasible they may be given by intravenous injection, as described by Dr. Barr. During operation, blood transfusions and plasma are probably best for maintaining ample protein reserve. In the postoperative period, many patients require protein by intravenous injection during the first eighteen to seventy-two hours in order to maintain a nitrogen balance. This may be accomplished by the intravenous use of blood plasma or amigen. Subsequently, the protein hydrolysate may be given by mouth; and after the use of the predigested foods for a short period regular foods, which may be classified as simple from the standpoint of digestion may be resumed.

In the past, there has been a tendency to overinvalidize surgical patients, and the long period of inactivity resulted in depletion of protein stores. The pendulum is swinging in the opposite direction; and although it is wise to reduce the period of inactivity to a minimum, we should not overlook the fact that these are not normal people. The inordinate loss of proteins in the postoperative period is controlled by the present trend to mobilize patients earlier and to make use of the predigested foods shortly after operation.

DR. SHORR: Dr. Glynn, what uses do you

make of protein hydrolysates in pediatric practice?

DR. MARTIN J. GLYNN, JR.: We encounter the same general indications for the use of protein hydrolysates as have been described for adult medical cases by Dr. Barr and surgical cases by Dr. Glenn. I should like to remark briefly about four conditions, perhaps more common in pediatric practice.

The youngster with severe diarrhea presents the most serious problem in which we turn to these agents. These cases are treated by prolonged starvation which in a young infant is a period of the order of two to four days. These youngsters appear to tolerate prolonged starvation quite well, but it is my impression, and that of other workers, that the use of protein hydrolysates is decidedly helpful. In the treatment of this condition, the first step is to restore the electrolyte pattern, the water balance and the plasma proteins to normal by the use of whole blood and plasma. After this is done and the circulation is in good condition, the protein hydrolysate may be given safely by hypodermoclysis. Specifically, the patient receives 40 cc. per Kg. of amigen 5 per cent in 5 per cent dextrose solution twice a day by hypodermoclysis in addition to 35 cc. per Kg. of 5 per cent dextrose solution by intravenous infusion twice a day. The treatment provides a total of 45 calories per Kg., 15 in the form of amino acid and 30 in the form of dextrose. This is by no means maintenance but it is a helpful step in that direction. I do not know of any studies on the fate of the amino acids which are provided by this regimen.

In eczema, we utilize amino acid therapy for a different purpose, namely, in an attempt to supply a source of protein with a minimum potential for allergic reactions. In severe eczemas, about 50 per cent may be expected to show considerable improvement and in some the control of the eczema

is complete. It is also worth trying in the mild eczemas of older infants. It is the impression of one observer, who tried it in mild eczemas of very young infants, that fewer of these developed severe eczema. The protein hydrolysate may be given parenterally but in eczema we are more likely to use it orally. We have used a mixture containing amino acids 20 per cent, carbohydrate up to 50 per cent, and fat 18 per cent, diluted so as to make an appropriate formula. Articles least likely to produce allergic reactions were used, in the case of the fat for example, olive oil, and in the case of the carbohydrate, arrowroot starch and dextrimaltose. Formulas based upon these materials can be made up in much the same way as the usual formula with milk so as to meet the requirements.

We occasionally use protein hydrolysates with advantage in the nephrotic syndrome. These patients often develop the so-called nephrotic crises, episodes of severe infection in the form of peritonitis, septicemia or both. We used it a great deal before the effective antibiotics were available; the intravenous amino acids seemed to influence the course favorably. A youngster who does not respond as expected to penicillin or sulfadiazine should be supported with protein hydrolysates.

There is a miscellaneous group of conditions in which amigen is often used by mouth with results that can be described as no more than encouraging. They include cases of young babies with persistent vomiting from obscure cause. A mixture containing amigen 3.5 to 5 per cent and 5 per cent carbohydrate may be given in such small amounts as are fairly well tolerated. It may be gradually replaced by the more sustaining types of nourishment. This mixture is also advocated for the first oral feedings after the therapeutic starvation in cases of diarrhea.

The other conditions, occasionally en-

countered in the pediatric group, are more frequently seen in adults such as postoperative troubles, trauma and burns. Their treatment is the same as in adults.

DR. BARR: It would be interesting to hear from Dr. Glenn about the use of amino acid mixtures in the treatment of burns. After a burn of moderate degree, a person may lose as much as 40 Gm. of nitrogen in twenty-four hours. The loss may continue during the ensuing days because of increased capillary permeability.

DR. SHORR: The subject is now open for general discussion. I saw your hand raised, Dr. Gold.

DR. HARRY GOLD: Could we have some discussion on the matter of the utilization of amino acids? There is abundant proof that their use can establish a positive nitrogen balance, indicating that nitrogen is being retained by the body. But what is the body doing with the nitrogen? Is it converting it into the proteins which are most needed? There is an infinite number of proteins, those of the skeletal muscles, liver, blood, heart muscle and many others. The loss of proteins in disease may be due to defective supply but it may also be due to defects in the bodily mechanisms for the synthesis of specific proteins, a defect which might not be corrected by any amount of extra supply. How does the evidence stand on some of these points? Suppose we first consider the question of regeneration of blood proteins in a case of hypoproteinemia.

DR. SHORR: I have the same questions. What actually happens to hydrolysates given intravenously to a patient with severe trauma, burn, shock, operative procedures or infection? Is there any evidence that the body utilizes the nitrogen? In what condition is it not utilized? Are we justified in assuming that what goes into the vein is actually available for the nutritional requirements of the patient, particularly the very ill patient whose needs are greatest?

DR. SAMUEL Z. LEVINE: It is my understanding that Dr. Whipple has shown that the amino acids are as satisfactory as plasma in raising the plasma protein levels in dogs which have been exsanguinated by his technic. Am I correct in that, Dr. Barr?

DR. BARR: When the level of blood protein has been artificially reduced by plasmapheresis or by inadequate diet, amino acid mixtures and plasma are exceedingly effective in raising the level of serum proteins. If, on the other hand, the low level of blood proteins is due to defective formation, as in disease of the liver, the administration of plasma or of amino acid mixtures does not correct the deficiency. Neither agent is more than moderately effective in the hypoproteinemia of nephrosis.

DR. GOLD: That seems to me to be a very important point to remember. We encounter many cases of hypoproteinemia, as in advanced heart failure, cirrhosis of the liver, and other conditions, in which an intensive course of treatment with amino acids has been given. It seems to get them nowhere because the liver seems to possess no power to synthesize the protein in these conditions.

DR. GLENN: In general, we have been unable to elevate serum proteins in patients by the intravenous administration of amino acids. I have the strong belief that we can prevent patients from failing by the use of amino acids when they are unable to take food. In a patient with a lowered serum protein value, the most effective way of elevating it is by means of blood transfusions and plasma.

VISITOR: Since there are these limitations in the effectiveness of protein hydrolysates, should we rely on such methods of alimentation, or is the use of whole blood or plasma always preferable?

DR. BARR: Experience indicates that with normal animals and with normal individuals it is possible to maintain nitrogen equilib-

rium and normal weight solely by means of protein hydrolysates. This does not mean that the same results will be obtained in a very sick person or in a person who has been damaged by shocking experiences. Nothing that we can do by such alimentation will maintain nitrogen equilibrium in a patient with a recent colectomy or other comparably severe operation on the gastrointestinal tract. There are some observations on patients immediately after appendectomies in which fairly small infusions of hydrolysates were able to maintain nitrogen equilibrium over six-day periods. On the other hand, in the same series, patients with colectomies, gastric resections or other serious operations, similarly treated, lost nitrogen in amounts up to 140 Gm. during the same period. These observations indicate that the response which is seen in normal individuals can be duplicated in patients only if the damage or shock has not been too great.

DR. SHORR: I think you have hit the point in cases that fail to respond. The nature and the degree of stress on the organism determine the response to intravenous alimentation. Studies have been carried out in severe infection and after trauma and it has been found that all the nitrogen administered as amino acids appeared in the urine in twenty-four hours. This went on for days. One might have an illusory feeling of comfort that protein has been supplied but there is clear evidence that it is being deaminated and does not remain as protein in the organism.

DR. BARR: Are there any comparable observations on the fate of protein itself?

DR. SHORR: Yes, there are for infusions of plasma. Here the protein remains in the body longer and is degraded by a slower mechanism.

DR. BARR: Is it not excreted as urea?

DR. SHORR: It is eventually but it is released apparently so slowly as to be more

available for the maintenance of nitrogen equilibrium.

DR. WALTER MODELL: Is there any difference in the time it takes to elevate the plasma protein level by means of amino acids and of plasma infusions, assuming, of course, a case in which either one or the other may do it?

DR. BARR: I do not think there is very much difference.

DR. SHORR: Might it not depend, Dr. Barr, on the state of the subject? In the normal animal in which the plasmapheresis experiments were conducted, all the normal capacities to synthesize proteins from amino acids were retained whereas in patients, suffering with a variety of infections or wounds, varying degrees of defects in the capacity for protein synthesis might obtain. Under such conditions the organism may hold on to injected plasma proteins so that the blood level can be satisfactorily raised, whereas injected amino acids may be much less efficiently utilized.

In relation to your point, Dr. Gold, that the retention of nitrogen after the administration of amino acids is an established fact, it is well to remember that in many cases neither oral nor parenteral administration of the usual amounts of protein in the diet gives rise to a positive balance. It is only after extraordinary amounts such as Co Tui, for example, used in his patients after gastrectomy, 350 to 450 Gm. of protein per day, that a positive balance appeared. As I have already indicated, in the patient with disease, receiving a parenteral infusion of amigen calculated to maintain a protein balance, every bit of the nitrogen often comes out in the urine within the same day in the form of ammonia or urea. There is a problem here which remains unsettled. Of course, it has nothing to do with the usefulness of this procedure as supplementary to oral feeding. But it does bring up the question of what is the nature of the disturbance

in disease which is responsible for such rapid breakdown and wastage of nitrogenous materials.

DR. BARR: I should like to hear from Dr. Shorr some comment as to the reason for the tremendous loss of protein which occurs following injury such as fractures, burns, acute infectious diseases or almost any other insult to the body. There are records of patients who during a ten-day period after operation have lost as much as 100 to 180 Gm. of nitrogen corresponding to 2.5 to 4.5 Kg. of muscle. A surprisingly great loss occurs often in uncomplicated anesthesia. Why should the body lose nitrogen under such circumstances?

DR. SHORR: It would be very nice if there were an answer. There are a number of possible explanations. One clinical observation may be cited, namely, that patients may or may not lose protein excessively under these circumstances and that, whether they do so or not, depends on their nutritional state; a highly undernourished individual may undergo an experience of this sort without loss of protein. Cuthbertson showed this very clearly in his experimental animals. Why does the debilitated individual not lose protein when the well nourished person may have a negative nitrogen balance of 30 Gm. on a daily ration of 150 Gm.? This possibly requires invoking the concept that there is one type of protein which is a little more specifically a part of the chemical structure of the cell, and another type which is, shall we say, in the nature of a reserve or depot protein in the old-fashioned sense. It would look as if the debilitated individual were down to his basic protein stores and for that reason does not readily lose more protein while the well nourished individual readily loses protein to the extent of his extra protein reserves. In addition, hormonal factors may play a rôle. This process which takes place in the course of the first three weeks after an

insult, such as infection or a fracture with recovery, may involve the action of hormones which have to do with protein metabolism and the reparative process, namely, the glycotropic and androgenic adrenal cortical hormones. It has been shown by Selye that, after any kind of stress or damage, an extraordinary change in the adrenal cortex takes place; it looks as if one had completely released its lipoids and with them its cortical hormonal content. Under the influence of stress, it is known that certain of these hormones are capable of breaking down protein excessively and forming carbohydrate from the non-nitrogenous residues. Support for this concept has been supplied for the human by Browne and his associates. These cortical hormones have been found by Venning and Browne in the urine in great excess after infections such as pneumonia, after operations, after fractures and, in fact, after all manner of stress and exposure.

Testosterone and its end products, the 17-ketosteroids, which we also measure in urine, have been demonstrated by Kenyon and others to promote the storage of proteins. Individuals who receive these androgens store protein unusually well, both normal individuals and those who have a lack of androgenic hormones such as hypogonadal males. It has been found that the level of 17-ketosteroids is characteristically low during the phases of an illness or damage when the level of adrenal cortical hormones is high. It looks as if these two factors, a depression in the elaboration of protein-storing hormones and an increase in the elaboration of protein-degrading hormones, may play a part in the unusual loss of protein during recovery.

DR. BARR: Much emphasis is now given to the loss of serum proteins which takes place during short periods. Surgeons, particularly, have regarded such loss as justifi-

cation for protein administration and for reasons which Dr. Glenn has brought out very clearly. One wonders, however, whether the consequences which are feared actually occur and whether it is so dreadful for the protein of the circulating blood to fall by 10 per cent, which will happen after forty-eight hours of starvation, and whether such a mishap must be corrected at once by the administration of plasma, albumin or amino acids. I doubt whether the actual necessity has been demonstrated but I should like to hear Dr. Glenn's opinion.

DR. GLENN: I think that the loss of a certain amount of protein in the normal individual, as Dr. Barr says, is probably not of great importance, but in an individual who is already depleted the further lowering may cause trouble and may account for the difference between a wound that will heal and one that will not. I believe that the intravenous administration of proteins exercises a type of sparing action.

DR. SHORR: I am inclined to agree that there is very little proof that a small reduction in blood proteins seen in surgical cases is of importance and that we may be going too far in our measures to correct them. It would seem reasonable, however, to attempt to restore blood proteins in cases in which they have fallen considerably. There is another question, however, which needs consideration, namely, how far we should go in attempting to establish a positive nitrogen balance in patients whose plasma protein levels are normal. Consider, for example, the patients with peptic ulcer who are now treated with amino acids. Vast quantities are necessary to establish a positive nitrogen balance in some of these. Is the positive nitrogen balance established in such cases beneficial to the course of the disease? I do not believe that we have the answer to this question. It certainly can be said that patients with fracture recover and

do extremely well at a time when they have regained only a small fraction of the protein lost during the illness.

DR. McKEEN CATTELL: The use of amigen has been extensively discussed. I want to ask whether other protein hydrolysates which are available are not equally satisfactory, or is there some preference for this particular brand.

DR. BARR: It is quite probable that the mixture which is called "Amigen" may be duplicated or improved. Many similar preparations have been offered and are now undergoing clinical trial. Since there are many pitfalls in the preparation of amino acid mixtures, actual clinical experience is needed with each new product and it is becoming increasingly difficult to find investigators who are interested in testing a new mixture to determine whether it is as good as one which is known to be satisfactory. Many tests are necessary. Ability to support normal growth must be demonstrated. Absence of immunologically active fractions must be established. Since mixtures of amino acids furnish an excellent culture medium, bacterial contamination must be excluded. Finally, the solutions must be free of pyrogens and other impurities. I mention these requirements to indicate how difficult it is to be sure that a new preparation of a protein hydrolysate is as satisfactory as one which has already been tested.

I think that Dr. Almy has had some experience with an acid hydrolysate.

DR. THOMAS P. ALMY: We used the preparation of Stearns and Company, parenamine 6 per cent, in two patients. It was well tolerated when injected at a rate similar to the rate at which we administer amigen. It is more acid than the parenteral amigen preparation; the pH is 5.5.

DR. SHORR: Perhaps Mr. Clarke, our pharmacist, would say something about the various preparations now available.

MR. DONALD A. CLARKE: The following

list of preparations is presented with the stipulation that it will probably be out-of-date in the near future, for not only are new preparations being added but the old ones are being altered.

I know of only two acid hydrolysates, parenamine (Stearns), made from casein, and aminosal (Abbott) made from beef-blood fibrin, both intended for parenteral use. No alkaline hydrolysate is available. All the others are enzymatic hydrolysates. Amigen (Mead Johnson) which is made from casein has already been mentioned. It is presently available only for parenteral use although the original preparation was also used orally. Their oral preparation is called protolysate, made from casein. Here is a partial list of other oral preparations: aminoids (Arlington) from milk, beef, wheat and yeast; aminoprote (U. S. Vitamin) from beef, casein, lactalbumin and yeast; lactamin (Wyeth) from lactalbumin; ledinac (Lederle) from liver; protein hydrolysate-MRT (Thompson) from yeast; protein hydrolysate (Squibb) from casein. Some of these preparations are already mixed with some form of carbohydrate. There are many other preparations not listed, which contain, in addition to hydrolyzed protein of some kind and carbohydrate, some other substances such as minerals, vitamins, flavoring materials and in one case, olive oil.

The parenteral preparations are usually provided as sterile solutions with added dextrose. Several concentrations of each are generally available, usually in the range from 5 to 10 per cent. The oral preparations are most commonly available in the form of a powder, some in the form of granules. Flavored solutions are obtainable and one manufacturer supplies an enteric-coated tablet.

DR. GOLD: It might be worth while calling attention to the fact that there are protein hydrolysates on the market sub-

stantially free of sodium chloride. This is of some importance in the problem of feeding a patient with congestive failure. I know of one such preparation, protein hydrolysate-MRT. It is not to be confused with the other preparation by the same manufacturer which contains 6 per cent sodium chloride. There is another preparation called protinal (National Drug) which is said to be very low in sodium chloride. There are other similar preparations.

In connection with the choice of preparations, it might be worth mentioning the experimental observation that the composition of a mixture of amino acids has a bearing on the extent to which it is utilized in the body to form proteins. It has been shown that if one omits an essential amino acid, an otherwise adequate mixture will fail to be utilized, and that the defect in utilization cannot be corrected if several hours elapse before the missing amino acid is supplied. This is a challenge to the preparations of protein hydrolysates; a proper mixture must be made available to the tissues at the same time if the mixture is to prove effective. This is perhaps one of the reasons why, as Dr. Barr has pointed out, it is necessary to test a new hydrolysate for its capacity to support growth. This may also have bearing on the question of the utility of protein hydrolysates in patients with evidence of protein deficiency who may be able to consume large quantities of proteins in the form of ordinary foods. We do not have satisfactory clinical evidence concerning this point; but it must be considered as a possibility that such patients may suffer with difficulty in protein digestion, so that an adequate mixture of amino acids does not become available in the blood stream, adequate in the sense of relative proportions of different amino acids being present at the proper time to enable the tissues to utilize them for the synthesis of tissue proteins.

DR. CHARLES H. WHEELER: From talking

with the house officers sometime ago, Dr. Barr, I gained the impression that they were still dissatisfied with the solutions of amigen. There were frequent pyrogenic reactions. Am I misinformed about that?

DR. BARR: When Elman started to use amigen, he encountered some quite alarming reactions consisting of fever, nausea and vomiting. As preparations improved and the rate of injection was slowed, he finally attained a record of the injection of many liters without any reactions. The absence of pyrogens in the solution and slow injection are factors of the greatest importance in the avoidance of reactions.

DR. LEVINE: The experience at Washington University has been very satisfactory. Intravenous and subcutaneous injections have been given to a large number of infants and young children without significant reactions. Our early experiences in smaller numbers were not so favorable. The children developed fever and some went into collapse. The house staff had become reluctant to use it. Matters have improved, however, with the more recent preparations and slower injections.

DR. GOLD: It seems from the literature that the number of serious accidents following parenteral amino acid injections is not very large. There was a report by Curreri and associates in the *Journal of the A.M.A.*, July 7, 1945, in which they encountered one fatality after about 2,000 administrations. The patient received the intravenous infusion of the usual preparation for two days without trouble but on the third day developed a shock-like reaction with hyperthermia and died forty hours later. They stressed the desirability of making someone in the hospital responsible for supervision of these infusions in order to insure that the solution is clear, that the rate of injection is slow, that the amino acid solutions are not mixed with materials of high pH, such as sodium salts of the sulfa drugs which give

rise to precipitation, and that the unused contents of the bottle which has been opened should be discarded. There seems to be the possibility that bacterial contamination in open bottles may give rise to toxic amines. Bacterial contamination is one of the points which Dr. Barr has stressed.

VISITOR: Has there been any sloughing in the case of the hypodermoclysis?

DR. GLYNN: We encountered one case of extensive sloughing in approximately 1,000 such treatments.

DR. GOLD: In regard to the toxicity of amino acids, you may be interested in some observations which were made by Riker and myself a few years ago in a study of sodium hydroxyacetate in which we also tested the amino acid, glycine. One is inclined to regard the amino acids as harmless since they are essential products of normal metabolism, however, we discovered that glycine may act as a poison in cats and dogs; as little as 1 Gm. per Kg. intravenously in cats gave rise to drooling, muscular weakness, hyperexcitability and dilatation of the pupils with failure to respond to light; and an oral dose of 6 Gm. per Kg. in a dog caused similar symptoms with convulsions and death in four hours. Clearly, the amino acids are not harmless substances.

DR. SHORR: What has been your experience with reactions, Dr. Almy, in the management of ulcerative colitis in which the intravenous route was used?

DR. ALMY: Our experience in one patient has been grim. Alimentation exclusively by intravenous route for a week resulted in thrombosis of all accessible veins. I was told by Dr. Albright that if one escapes this difficulty, one may begin to see remission of the acute symptoms with this treatment after one week.

DR. BARR: It might be interesting to hear of Dr. Almy's experience with the oral use of the amino acids in ulcerative colitis. The discussion thus far has dealt chiefly with in-

travenous alimentation which, perhaps, has less application than the oral route.

DR. ALMY: In ulcerative colitis, the intravenous administration of hydrolysates has always appeared more attractive because of the fact that it avoids the use of the colon as a conduit of food residue, however, we have tried large amounts of the hydrolysate orally in these protein-starved patients. We gave them 5 to 6 Gm. of amigen per Kg. per day by mouth, together with dextrimaltose in a manner comparable to that used by Co Tui in the treatment of peptic ulcer. The results were not as striking as I had hoped they would be. In a small group of a dozen patients, 30 per cent showed a rapid gain in weight to the extent of about 3 to 5 Kg. and progressive improvement resulted. The other cases remained uninfluenced. This form of alimentation caused severe diarrhea in these patients and it is noteworthy that in spite of it the gain in weight took place.

VISITOR: How successful is the retention enema of amigen?

DR. FREDDY HOMBURGER: We have been using retention enemas of a Squibb casein hydrolysate which is roughly comparable to amigen and, when given with proper technique and care, have achieved positive nitrogen balance over a fairly long period of time. It was not found possible to achieve this in all patients but in about one-third of the patients it was successful.

DR. SHORR: And what is the proper technique?

DR. HOMBURGER: The rectum should first be cleansed very carefully with a small water enema. Only small quantities at a time should be used. Instead of the ordinary rectal tube a urethral catheter should be inserted to about 10 or 12 inches. We use a Murphy drip for about one to two hours to give 400 cc. of the solution which contains about 100 to 150 Gm. of hydrolysate in 5 per cent dextrose. Usually the first day there

is some irritation; but when the patient is accustomed to the procedure, the enema may be retained and nitrogen balance may be maintained.

DR. SHORR: Where do you think the resorption takes place? In what part of the large gut?

DR. HOMBURGER: I think that the resorption takes place in the lower portion of the large intestine where water is known to be resorbed.

DR. SHORR: Not in the rectum?

DR. HOMBURGER: In the sigmoid, I think. We have evidence only for the fact that the nitrogen contained in the administered material is retained.

DR. GOLD: The protein hydrolysates may therefore be given by various routes, oral, subcutaneous, rectal and intravenous. There are reports of its satisfactory use by the intrasternal route directly into the bone marrow by means of the Turkel needle. The needle may apparently be left in place for twenty-four hours or longer and the material may be administered as rapidly by this route as by the intravenous route, about 1 to 2 Gm. of amino acid nitrogen per hour.

DR. SHORR: This is an extensive subject and there are many more points which need to be considered but our time is up. Perhaps the interesting topic of protein hydrolysates in peptic ulcer may be taken up at another conference.

SUMMARY

DR. GOLD: We may now bring together a few of the salient points which were elaborated in the conference this afternoon. A disorder of protein metabolism seems to be extremely common in diseases, injuries and other states of bodily stress, such as infections, operations, anesthetics, malignancy, burns, hyperthyroid states, diarrheas and prolonged inactivity. It is clearly manifest when there is extensive body wasting, but it is earlier detected by an increased loss of

nitrogen of varying degrees often reaching alarming proportions. The circumstances are frequently such that an adequate supply of proteins in the form of the usual foods and the use of the regular channels for their consumption are not feasible. Great interest has, therefore, been aroused in the discovery about ten years ago that it is possible to prepare appropriate mixtures of amino acids in the form of protein hydrolysates, suitable for all the common routes of administration, and to use them as a source of bodily proteins. It appears to be a development of major importance, the culmination of experiments covering a period of nearly forty years. It supplies the missing link, the protein, the others being carbohydrates, fats and vitamins, in the long quest for complete intravenous alimentation.

There was not sufficient time to consider all the conditions in which the protein hydrolysates may be applied, but the discussion indicates that they have already been put to use extensively in a wide variety of conditions associated with an unfavorable protein balance. In the conference, the surgeon discussed their uses preoperatively and postoperatively in relation to extensive surgical procedures, traumas, hemorrhage and anesthesia. The pediatricians discussed their value in the treatment of diarrheas of infants, in the nephrotic syndrome and in eczema as a source of protein with minimum potential for allergic reactions. They seem to be of great value in patients with burns who lose alarming quantities of protein, of some value in edema associated with hypoproteinemia, in ulcerative colitis, peptic ulcer and in nutritional problems in which only parenteral alimentation is feasible. This is but a small part of the list of conditions in which the protein hydrolysates have been recommended and used as a means of promoting recovery from states of ill health.

Enthusiasm for the use of protein hydroly-

sates has naturally run very high; and as experience has increased and the problem has received more intensive consideration, numerous questions have arisen. How strong is the evidence for the utility of the protein hydrolysates in a large proportion of the conditions in which they are now used? Are we assigning too many troubles to the moderate reductions in blood protein levels and negative nitrogen balance which occur so commonly? Is the zeal for establishing nitrogen equilibrium or positive nitrogen balance in many of the conditions in which they are now used justified by the results? Since such restorations seem theoretically correct, there is the danger of carrying the application of protein hydrolysates far beyond the point of satisfactory evidence that they are actually useful.

On the theoretical side such questions have been raised as to what the body does with the amino acids administered in the form of protein hydrolysates. In normal individuals, the evidence is strong that, when they are administered sufficiently slowly and in proper composition, they are stored and converted into proteins; but much remains to be learned about abnormal states in which the basic difficulties may lie in defective mechanisms for converting amino acids into the infinite number of proteins. Then there is the question whether the administration of hydrolysates serves merely to spare body proteins or whether they exert some other type of beneficial actions. Why does the body lose protein so rapidly in such conditions as protracted bed rest, anesthesia and operative procedures in which there may be apparently little blood loss or tissue destruction? An interesting viewpoint was presented to the effect that an endocrine imbalance involving the cortical hormones of the adrenal and the androgens may be responsible for the marked loss of proteins in certain states of bodily stress.

The answers to some of these questions have not been entirely satisfactory, but the exploration of these and others in the discussion this afternoon has helped to reveal the complexity of the problem and to provide some insight into the reasons for the numerous failures to accomplish expected results. In disease states, the simple loading of the system with amino acids falls far short of correcting many of the conditions. It was pointed out, for example, that hypoproteinemia in surgical problems is much more often corrected by plasma or blood infusions than by intravenous hydrolysates; and that in the prolonged starvation in infant diarrhea, it is imperative first to restore the blood protein level by plasma infusions before attempting to maintain the gains by parenteral protein hydrolysates. Much careful observation will be necessary properly to sift out the practical from the large volume of theoretical indications.

The parenteral administration of protein hydrolysates is not without risks. The improvement in the preparations of commerce and the slowing of the rate of administration have greatly reduced serious accidents although minor unpleasant reactions are fairly common. Suggestions have been made for avoiding disasters in the routine use of intravenous protein hydrolysates in hospital practice.

The choice of preparations is of considerable importance, especially in relation to those for intravenous injection. Many of the preparations now on the market show great improvement in composition, freedom from pyrogens and allergenic peptides, but the matter of preparations is in a state of constant flux; the ideal preparation is not yet available.

The discussion also includes such topics as a formula for complete intravenous alimentation, dosage for oral use and the various routes of administration.

Hydrohemothorax and Peripheral Vascular Collapse*

STENOGRAPHIC reports, edited by Robert J. Glaser, M. D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. K. (B. H. No. 137472), a seventy-two year old white, unemployed male, entered the Washington University Clinics on July 3, 1946, complaining of cough. The family history was entirely normal. The past history revealed that in his youth, the patient had had measles and, for a month thereafter, a severe cough. Since that time he had been subject to upper respiratory infections which were usually associated with cough. The patient first had malaria when thirty-six years of age and then had had several subsequent attacks. At the age of forty-seven, he contracted typhoid fever but made an uneventful recovery. He always had been obese and at one time weighed 274 pounds. He had worked in a machine shop until forced to retire one year before admission because of his age. His habits were good.

Two months prior to entry, the patient was out in the rain for several hours; that night his chest felt somewhat "tight" and he wheezed slightly. He then developed a persistent cough, productive of small amounts of frothy sputum which was sometimes "tinged with pink" and occasionally contained a little gross blood. The sensation of tightness in the chest increased and wheezing became audible; the patient was of the

opinion that the wheezing originated in the right side more than in the left side of his chest. He had no pain but noted increasing shortness of breath on exertion and after coughing. His appetite steadily failed and he began to have night sweats. Since the onset of his illness, he had lost 14 pounds.

Physical examination on entry revealed the temperature to be 36.8°C., the pulse 88, respirations 22, and blood pressure 140/100. The patient was markedly obese; he wheezed audibly on expiration but was not orthopneic. The pupils reacted normally; the fundi showed some arteriolar narrowing. The ear drums were retracted and hearing was slightly impaired. There was a large perforation of the anterior nasal septum and the nasal mucosa was red and edematous. The tonsils were atrophic. The trachea was in the midline. The right side of the chest appeared to be flatter than the left and moved less well. There was flatness to percussion over the lower half of the right chest anteriorly and posteriorly; over this area tactile fremitus was lost and breath sounds were absent. Breath sounds were bronchial in quality over the right upper lobe anteriorly. The spoken voice was diminished over the right lower lobe and had a nasal quality; the whispered voice was

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absent. The cardiac apical impulse was not felt and the left border, which was percussed with difficulty because of the patient's obesity, extended approximately 13.5 cm. to the left of the mid-sternal line in the fifth interspace. The rhythm was regular; the sounds were very distant but P_2 was greater than A_2 . The abdomen was pendulous but no organs or masses were detected. In the left upper portion of the prostate a small, very firm, non-tender nodule was palpable. The deep tendon reflexes were hypoaactive.

A roentgenogram of the chest was reported as follows: "There is fluid in the right pleural cavity up to the third interspace; the heart is shifted to the left. The left chest is clear."

The patient returned to the Clinic three days after his first visit; a thoracentesis was performed and 1,300 cc. of serosanguineous fluid were removed from the right chest. The fluid did not clot; it contained 35,000 cells without acid and 1,300 cells with acid; the differential count showed 52 per cent lymphocytes, 16 per cent segmented forms and 32 per cent large mononuclear cells.

The patient again returned to the Clinic three days later in apparent shock. He was immediately admitted to the Barnes Hospital. No further history was available.

At the time of entry, physical examination revealed the temperature to be 36.5°C ., the pulse 110, respirations 40 and the blood pressure 80/0. The patient was pale, perspiring and markedly dyspneic and orthopneic. He talked in gasps but the effort seemed to exhaust him. The trachea was displaced to the left. An inspiratory wheeze was audible and expiration was forced. A paradoxical pulse was present. The liver edge was felt 2 cm. below the costal margin and was slightly tender. There was pretibial edema. The remainder of the physical examination was unchanged from that recorded previously.

The laboratory findings were as follows:

Blood count: red cells, 5,240,000; hemoglobin, 15 Gm.; white cells, 19,650; differential count: segmented forms, 77 per cent; lymphocytes, 12 per cent; monocytes, 11 per cent. Urinalysis: albumin, normal; sediment: many hyaline, finely granular and waxy casts; 20 to 30 red blood cells per high power field. Blood Kahn reaction: negative. Roentgenogram of the chest: "There is some increase in fluid in the right pleural cavity since the previous film. A fluid level is seen within the circle of the first rib. There is little displacement of the mediastinum; the cardiac shadow is enlarged." Electrocardiogram: Low voltage in all complexes; T waves iso-electric in leads I, II, and III; Q wave in leads III and CF IV.

Immediately after entry, a thoracentesis was performed; after 1,250 cc. of serosanguineous fluid were removed from the right chest, the patient became more dyspneic and anxious and the procedure was discontinued. The fluid had a specific gravity of 1.014; it contained 70,000 red cells and 2,050 white cells. The differential count showed 3 per cent segmented forms, 95 per cent lymphocytes and 2 per cent large mononuclear cells. The protein content was 2.4 Gm. per cent. Microscopic sections of the cell block sediment (reported after death) revealed epithelial cells which formed acini. Roentgenogram of the chest, obtained following the thoracentesis, was reported as follows: "There is a large amount of fluid in the right chest; the trachea is deviated to the left in its upper portion and to the right in its lower portion. The heart is unchanged in appearance from the previous film. The left chest is clear."

Following the thoracentesis the patient continued to be markedly dyspneic and orthopneic; he was given 30 mg. of morphine sulfate in divided doses and was placed in an oxygen tent. The heart sounds became inaudible; the pulse was thready but definitely paradoxical. The respirations

became progressively more difficult and rapid. Twelve hours after admission another thoracentesis was done on the right, and 600 cc. of serosanguineous fluid were removed without obvious benefit to the patient. A pericardial paracentesis was attempted and 50 cc. of bloody fluid were withdrawn; the fluid did not clot. The patient continued to fail and died twenty-four hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents two major problems: The first concerns the nature of the primary disease and the second the explanation of the terminal events. When the patient first came to the Clinic, he was not desperately ill; he became so, however, several days later and died within a week. Dr. Flance, what primary diagnosis would you attach to this man's illness?

DR. I. JEROME FLANCE: Considering the patient's age, his history and the fact that he had a bloody pleural effusion, it seems likely that he had a malignancy and one would certainly consider the possibility of primary carcinoma of the lung.

DR. ALEXANDER: Dr. Dammin, would you describe the microscopic section made from the cell sediment of the pleural fluid?

DR. GUSTAVE J. DAMMIN: One sees two types of cells in the section. (Fig. 1.) The darker staining cells appear to form acini and thus strongly suggest a malignancy. The lighter cells with large pale nuclei constitute the normal lining of the pleural surface. In our opinion, the most likely diagnosis is that of a malignant tumor involving the pleural cavity.

DR. ALEXANDER: Dr. Flance, would you comment on the type of tumor which this man may have had?

DR. FLANCE: Primary adenocarcinoma of the lung usually does not occlude a major bronchus whereas squamous cell carcinoma

may well cause bronchial obstruction. The signs described in the physical examination would have been compatible with bronchial obstruction in addition to pleural effusion.

DR. ALEXANDER: Is adenocarcinoma the most common type of primary lung tumor?

DR. FLANCE: No, epidermoid carcinoma is most frequent. The fact that such tumors often arise around a major bronchus explains why they may ultimately lead to obstruction and atelectasis.

DR. ALEXANDER: I understand that you assume that the pleura was invaded by a tumor which was primary in the lung. Have you considered a primary endothelioma of the pleura?

DR. FLANCE: It is an extremely rare tumor.

DR. ALEXANDER: I agree that it is most likely that this man had a bronchogenic carcinoma which invaded his pleura and gave rise to the effusion. A thoracentesis was performed and 1,300 cc. of fluid were removed. Three days later, when the patient was admitted to the hospital, another thoracentesis was begun and 1,200 cc. of fluid were removed before the procedure had to be interrupted because of increasing dyspnea and apprehensiveness. Is rapid reaccumulation of fluid common in a situation such as was presented here?

DR. FLANCE: Patients with metastases to the pleura may reaccumulate fluid with striking rapidity.

DR. ALEXANDER: Is not the fact that the effusion was bloody of great significance in regard to prognosis?

DR. KEITH S. WILSON: A number of studies have shown that most bloody pleural effusions are due to malignancy involving the pleura. A certain number arise as a result of direct trauma or rupture of a vessel and rarer causes include tuberculosis and acute infections of the lung.

DR. ALEXANDER: Turning to the events which led to the patient's admission to the

hospital, it will be remembered that when he returned to the Clinic for the third time, his condition had become grave; indeed, he was described as being in shock. Dr. Wilson, I believe you saw him at that time. Would you comment?

DR. WILSON: He certainly appeared to be in a state of peripheral vascular collapse. We felt that in all probability he had a pericardial effusion, probably with tamponade.

DR. ALEXANDER: Dr. Bottom, do the x-ray findings contribute to the solution of the problem here?

DR. DONALD S. BOTTOM: The second film was obtained with portable equipment and was not very clear but the heart did not seem to be larger than it was on the previous films and the mediastinum did not appear to be shifted.

DR. ALEXANDER: Dr. Schroeder, do you believe that a massive pleural effusion may give rise to signs simulating cardiac tamponade?

DR. HENRY A. SCHROEDER: No, I do not think so, especially if the mediastinum is not shifted.

DR. ALEXANDER: Dr. Wilson, what signs pointed to cardiac tamponade?

DR. WILSON: The inaudible heart sounds, paradoxical pulse and shock-like state all suggested that diagnosis.

DR. ALEXANDER: Dr. Erlanger, would you discuss the electrocardiogram? Does it give any indication of cardiac tamponade?

DR. HERMAN ERLANGER: The most striking thing about the electrocardiogram was the extremely low voltage; the T waves throughout were flat. The extremely low voltage and the flattening of the T waves are both consistent with a diagnosis of pericardial effusion and taken together with the physical signs and the patient's clinical condition are certainly significant. If the patient had had pericarditis, elevation of the S-T segments with inversion of the T waves might have been present.

VISITING PHYSICIAN: Were the patient's veins distended?

DR. WILSON: The patient was quite obese and neck vein distention could not be demonstrated.

DR. ALEXANDER: Is venous distention prominent in acute tamponade?

DR. WILSON: Frequently it is not; the venous pressure should be measured in order to determine increased venous pressure; often, as was true here, patients are so dyspneic and apprehensive that accurate determinations cannot be made.

DR. ALEXANDER: In chronic constrictive pericarditis there are adhesions about the vena cavae causing the venous pressure to be elevated, but in acute tamponade I am not quite certain as to the mechanism. The pericardium does not extend far over the veins entering the right auricle and one must consider pressure on the auricle itself.

DR. WILSON: In chronic constrictive pericarditis, I would expect the venous pressure to be considerably higher than in acute cardiac tamponade.

DR. SCHROEDER: One must take into account the amount of fluid remaining in the peripheral vascular system at the time of the cardiac accident. For example, in cardiac failure associated with coronary artery occlusion, the venous pressure may not be elevated at the onset, but as time goes on, especially in the presence of severe occlusion, and the patient retains salt and fluid, the amount of fluid in the periphery increases and the signs of congestive failure appear.

DR. DAMMIN: Do you interpret the palpable liver and the pretibial edema as evidence of impaired return of blood to the right heart?

DR. SCHROEDER: Yes.

DR. HENRY H. GRAHAM: Three days before entry, when the patient was examined in the Clinic, his liver was not palpable and he apparently had no edema; he did, however, have edema when admitted to the hospital.

VISITING PHYSICIAN: If this patient had not been in shock when he came in, his venous pressure might well have been elevated.

DR. SCHROEDER: That is a very well taken point. The extra fluid may have been in his capillaries.

DR. SAMUEL C. BUKANTZ: I think we should consider the large amount of fluid in his right chest as possibly accounting for the low circulating volume, especially if the effusion represented a recent and fairly rapid accumulation.

DR. ALEXANDER: The patient had a total of about 2,500 cc. of fluid removed from his chest. I do not know whether this amount could have been a factor in his low circulating blood volume. What is your opinion, Dr. Schroeder?

DR. SCHROEDER: It is difficult to say. I think that this loss of fluid from his vascular system would have been replaced by congestive fluid. However, if the patient had received no fluid by mouth or vein, he may well have been dehydrated.

DR. ALEXANDER: Are there any other suggestions to explain the acute episode which lasted only twenty-four hours and terminated in the patient's death?

DR. PALMER H. FUTCHER: I think of one alternate possibility—coronary occlusion. This man was seventy-two years old and was certainly a candidate for coronary artery disease; I do not believe that the electrocardiogram rules out the possibility of an acute myocardial infarction.

DR. ALEXANDER: How would you explain the pericardial fluid which apparently was not present one week prior to death?

DR. FUTCHER: If the patient had had a coronary occlusion, he might well have had a small amount of pericardial fluid in association with the acute episode. Only 50 cc. of fluid were withdrawn from the pericardium; such an amount, if indeed that is all

there was, would have been insufficient to cause tamponade.

DR. ALEXANDER: Dr. Graham, are you satisfied that there were only 50 cc. of fluid in the pericardium?

DR. GRAHAM: No, I am sure there was much more.

DR. ALEXANDER: What alternate explanation do you offer for the pericardial fluid?

DR. FUTCHER: The patient may have had local involvement of the pericardium by tumor; it is also conceivable that the needle was not in the pericardial sac when the 50 cc. of fluid were withdrawn.

DR. ALEXANDER: Certainly, a tumor of the lung may have metastasized to the pericardium and given rise to an effusion.

DR. FUTCHER: In considering the origin of metastatic carcinoma, two sites come to mind, neither of which seems as likely as the lung. First, the presence of red cells in the urine suggests a renal cell carcinoma. Secondly, a small nodule was described in the prostate and conceivably the patient may have had carcinoma of the prostate with metastases.

DR. ALEXANDER: I think both of your suggestions merit consideration. Hypernephroma, which so frequently metastasizes to the lungs, is particularly worthy of consideration.

DR. SCHROEDER: Could we have additional information regarding the nature of the fluid taken from the pericardium?

DR. GRAHAM: The fluid looked like pure blood but did not clot.

DR. ALEXANDER: Are there further suggestions?

DR. ERLANGER: There is one further comment which I would like to make. The electrocardiogram does not rule out the possibility of myocardial infarction. In the early stages of an infarct, the electrocardiogram may show very little change other than low voltage.

DR. ALEXANDER: In summary, it seems most likely that this patient had a bronchogenic carcinoma which metastasized to the right pleural cavity and probably to the pericardium; the pericardial metastases produced an effusion and subsequently cardiac tamponade of rather sudden onset. Acute myocardial infarction has been mentioned as a possible explanation of the terminal episode and the kidney and prostate were listed as possible primary tumor sites.

Clinical Diagnoses: Bronchogenic carcinoma with metastases to the right pleural cavity and the pericardium; pericardial effusion and acute cardiac tamponade; ? myocardial infarction; ? hypernephroma; ? carcinoma of the prostate.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: The right pleural cavity contained 300 cc. of blood-stained, cloudy fluid. In the right upper lobe there was a marked retraction of the pleura over an area approximately 1 cm. in diameter. The cut surface through this area revealed a grayish, granular tumor mass lying immediately beneath the retracted pleura, and a white zone of induration extended toward the hilus also involving the mediastinum. The main stem bronchus was narrowed by a thickened, indurated wall but the mucosa, as far as it could be traced, was intact. A small bronchus, approximately 1 mm. in diameter, entered the tumor mass and ended in an area of necrosis. A lingular process of the right lobe was cut off by fibrous scarring and the area was reddened and firm. A small artery leading to this region was found to contain a grayish-red thrombus. The left lung showed many areas of atelectasis.

The pericardial sac contained 1,500 cc. of grossly bloody fluid which did not clot. The parietal layer was continuous with the tumor mass in the mediastinum and its surface was covered with a shaggy fibrinous

exudate. When the exudate was removed, the surface was finely granular with many grayish white nodules and extensive areas of ecchymosis. There were two nodules noted in the liver and a single small nodule in the cortex of the right kidney. They were interpreted as representing metastatic tumor.

In the posterior lobe of the prostate, there was a firm, yellowish white nodule measuring 2 by 1 by 1 cm. On cross section, it was homogenous and sharply demarcated from the surrounding tissue.

DR. ROBERT A. MOORE: Quite aside from answering some of the specific questions raised in the clinical discussion, such as the cause of the pericardial effusion, the essential task of the pathologist in analyzing this case is to determine the primary site of the tumor. Manifestly, there was a tumor in the lung and about the right hilus which exhibited many of the characteristics of a primary carcinoma of the bronchus or lung. Certainly, from the standpoint of gross appearance, it might have been either one of two types of carcinoma; that is, a bronchogenic carcinoma or one of the so-called peripheral lung tumors. The latter are characterized by depressed, radiating surface scars, the tumor lying just beneath the scar. An interesting question concerning the origin of such tumors arises, for when one has seen several of them he is not at all convinced that the tumor can produce as much scarring and retraction of the pleura as is characteristically seen; hence the possibility that a peripheral lung tumor originates in a pre-existing scar must be considered.

Turning to the prostate gland, the gross appearance of the nodule in that structure also bore the characteristics of a primary tumor. It was located in the posterior lobe of the gland, was unilateral, and was of a size consistent with many occult carcinomas of the prostate. Our major problem, then, was to determine whether this man had two

primary tumors, or whether he had one tumor which metastasized to several other organs. If one assumes that there was a single primary tumor which arose in the lung, could the nodule in the prostate have represented a metastasis? Such an explanation is most unlikely for metastatic carcinoma of the prostate is practically unknown. Occasionally metastases of the prostate are seen when the organ is invaded by tumors arising in nearby structures; that is, the rectum, the bladder or from reflections of the peritoneum. But an actual carcinoma nodule in the prostate, metastatic from a distant organ is an extreme rarity, almost as rare as primary carcinoma of the seminal vesicles of which, I believe, there are some seven or nine cases in the world literature. I have read all of those reports and on the basis of the description given have my doubts as to whether any actually were primary in the seminal vesicle. The converse explanation, that is, that the tumor was primary in the prostate and metastasized to the lung, liver and kidney must also be considered. In order to attempt to reach a final conclusion, we must rely on the microscopic sections and examine the histologic structure and the appearance of the lesions.

The first section (Fig. 2) is from a bronchus surrounded by tumor. The mucosa is in large part replaced by tumor; there are a few islands of normal glands remaining. The tumor lies outside the muscularis; as Dr. Johnson pointed out in the gross description, no ulceration of the mucosa could be detected and in those sections which have been examined microscopically, the epithelium of the surface is intact. Now that observation has an important bearing on our final conclusion, particularly if it holds for all of the mucosal surface. Carcinoma of the bronchus originates from surface epithelium rather than from the glands themselves; and if intact surface epithelium exists over the

entire extent of the tumor nodule in the lung, a serious doubt would arise that the tumor represented a primary carcinoma of the bronchus, at least of the type usually seen.

There are certain organs in the body that give rise to tumors which produce mucin; such tumors arise from cells which themselves are capable of producing mucin. There are certain other organs whose cells do not possess this characteristic. We are fortunate here in dealing with bronchus and prostate. Mucinous carcinoma of the prostate does not exist because the prostatic epithelial cell does not have the capacity, under any circumstance, to make mucin. On the other hand, primary carcinoma of the bronchus is frequently of the mucinous type, though not exclusively so. Adenocarcinoma of the lung, the type seen here, occasionally does not produce mucin. Mucicarmin stains demonstrate that the tumor cells are free of any intracellular mucin. The cell itself is of a type consistent with an origin either in the bronchus or prostate; there is nothing in the histologic appearance which points to one or the other with any certainty. If, as are 35 to 40 per cent of all primary malignancies of the lung, this tumor were an epidermoid carcinoma, the problem would be simple for an epidermoid carcinoma of the prostate is an extreme rarity. I believe there are forty or fifty cases reported in the literature; perhaps all of these arise from the prostatic utricle and not from the prostate itself. They are relatively benign and metastasize late.

In the next section (Fig. 3), lung, pleura and a mediastinal node are shown; the tumor has invaded both the node and the pleura and has obliterated the pleural cavity on the medial side of the lung. In Figure 4, the periphery of the lung is seen; the section represents an excellent example of lymphatic invasion in the pleura by adenocarcinoma. The tumor exhibits a moderately anaplastic character in that

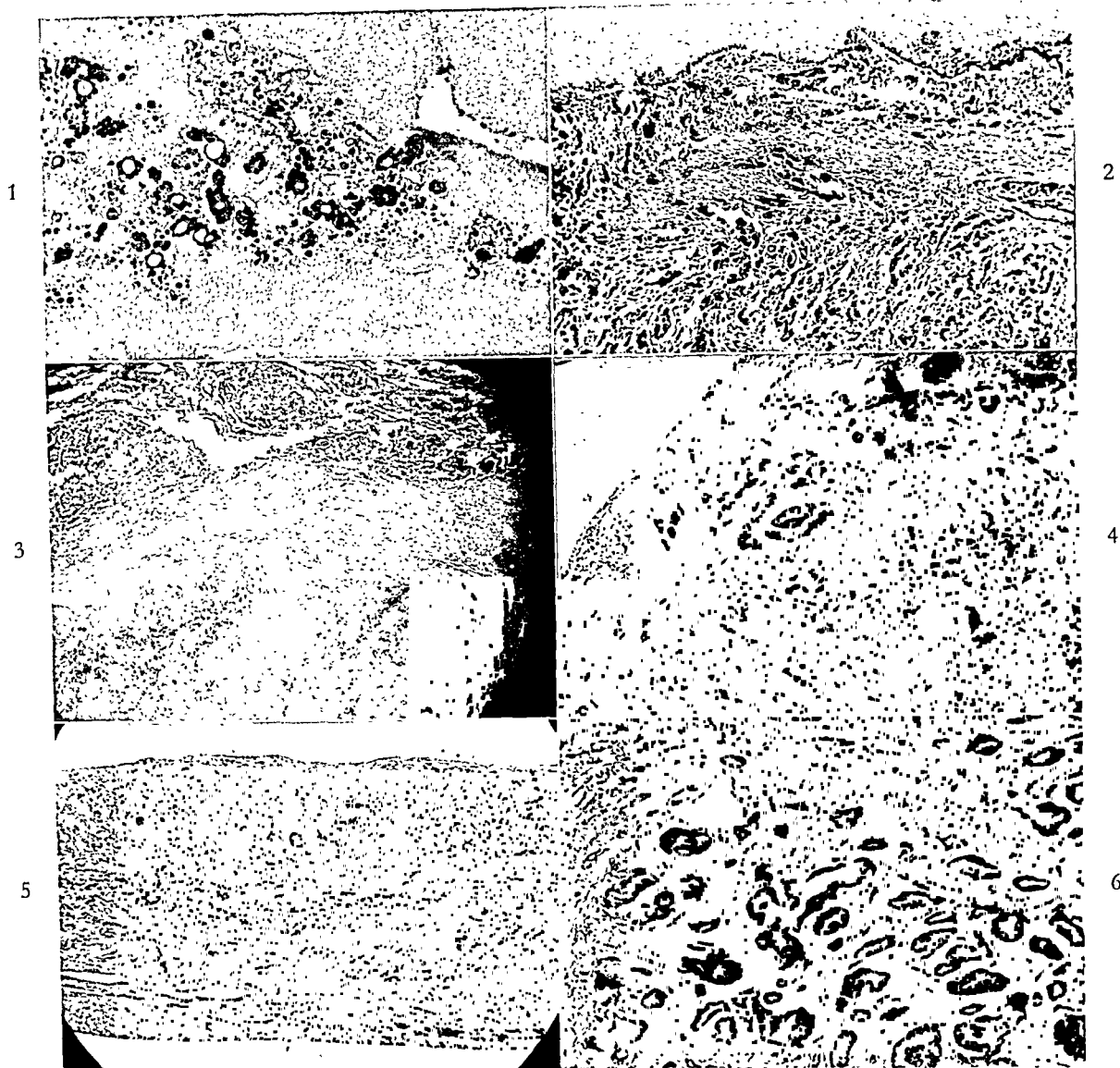


FIG. 1. Section of cell block made from pleural fluid. Note the tendency toward acinar formation.

FIG. 2. Section showing a bronchus surrounded by tumor.

FIG. 3. Section showing the lung, pleura, and a mediastinal node involved by tumor.

FIG. 4. Lymphatic invasion by adenocarcinoma in the pleura.

FIG. 5. Section showing invasion of the pericardium by tumor.

FIG. 6. Section of the primary carcinoma in the prostate. Note that many of the glands have pulled away from the basement membrane.

there is a slight to moderate amount of connective tissue in between the tumor cells. Figure 5 shows a section of the pericardium and pleura. The tumor has invaded the pericardium and the invasion is certainly an adequate explanation of the origin of the pericardial effusion. When the pericardium is invaded by tumor there may be a variable

amount of fluid in the pericardial sac. In this instance, you remember 1,300 cc. were found.

Finally, the section of the prostatic nodule (Fig. 6) could not be a more typical example of primary carcinoma of the prostate. The tumor is composed of acini of variable size and structure. They are composed largely

of basophilic cells and there is little evidence of secretion. The connective tissue of the stroma of the prostate is not greatly altered. A point that is extremely valuable, but not diagnostic because it is an artefact, is that many of the glands are pulled away from the basement membrane. This feature is highly characteristic of carcinoma of the prostate. I lay great weight on the presence of this artefact in making a microscopic diagnosis of carcinoma of the prostate. In some way the epithelial cells of a carcinoma of the prostate respond differently than other cells to the agents used in the preparation of microscopic sections; that is, to formaldehyde, to dehydration in alcohol and to heating. This phenomenon is not seen when celloidin sections of carcinoma of the prostate are prepared.

To return to the question of the origin of the primary tumor in this case, we must accept the carcinoma of the prostate as being primary. The tumor exhibits all of the characteristic gross and microscopic findings. It is well known that primary carcinoma of the prostate may be occult and yet may give rise to metastases which, in size, extent and in production of clinical symptoms, may be all out of proportion to the size and extent of the primary tumor. There is a generally accepted dictum which we have pointed out at these conferences previously, namely, that in attempting to establish whether in a given case there is one or two tumors, the burden of proof is on the individual who says there are two tumors. We can muster few positive facts to support the concept that there was a primary carcinoma of the bronchus. We conclude, therefore, that the patient had a primary carcinoma of the prostate with metastases to the lung, hilar lymph nodes, pleura of the right lung, mediastinum, pericardium, liver and right kidney.

One point concerning the metastases should be made. From time to time, we have

suggested the value, in differential diagnosis, of the location of metastases. This patient had metastases to the liver and the right kidney which would be more characteristic of carcinoma of the bronchus than of carcinoma of the prostate. As I have also pointed out before, however, all deductions based on differences in the distribution of metastases of carcinoma of the lung in contrast with other carcinomas are non-operative as soon as the latter metastasize to the lung, for then secondary metastases may arise in the same distribution as those from a primary carcinoma of the bronchus. The primary tumor in this case, therefore, despite the fact that it arose in the prostate, having gone to the lung, may then have metastasized further to any other organ.

In regard to the heart, it weighed 420 Gm. The patient weighed 97 Kg. and it would be difficult to establish a diagnosis of hypertrophy of the heart in view of the total body weight. Perhaps there was slight cardiac enlargement but it was certainly not striking. Considering the question of the presence or absence of cardiac failure, we observed at autopsy slight edema of the extremities and chronic passive congestion of the liver and spleen; these findings could not be accounted for on the basis of the right hydrothorax. We would, therefore, conclude that the patient had an element of congestive failure and that presumably it was caused by the accumulation of 1,300 cc. of fluid in the pericardial sac. He had only slight arteriosclerosis of the coronary arteries and there was no evidence in the myocardium that he had suffered coronary insufficiency. Finally, as to the presence of red blood cells in the urine, we suspect that that finding was of no significance except to make the clinicians' problem more difficult, for in our examination to explain the hematuria the only finding, either grossly or microscopically, were a few petechiae in the medulla of the kidney. Why they were there,

I do not know, unless they can be explained on the basis of cardiac failure.

DR. ALEXANDER: Dr. Moore, because of your very extensive experience with carcinoma of the prostate, I should like to ask, first, the incidence of involvement of the lung by carcinoma of the prostate, and secondly, whether you would consider unilateral involvement of the lung unusual?

DR. MOORE: It is unusual, Dr. Alexander, for carcinoma of the prostate to produce the type of metastasis such as you saw here, that is, a mass in the mid-zone of the lung extending into the mediastinum. We have mentioned on occasion that one basis for distinguishing a primary carcinoma of the lung from other tumors is the occurrence of metastases to a regional node. At a reasonably early stage in the disease, metastatic carcinoma arising in other organs will appear in the lung but not in the regional

node, while at the same stage the primary tumor of the bronchus will have metastasized to the regional node. The metastasis seen here is unusual for a tumor having arisen elsewhere and I cannot, therefore, absolutely deny that this man did not have two tumors, one of which was in the bronchus. However, I can marshall no objective positive evidence to support such a concept and, therefore, on the thesis that the burden of proof is on the pathologist who says there are two tumors, we concluded that there was only one.

Anatomic Diagnoses: Carcinoma of the prostate; metastatic carcinoma involving the lung, hilar lymph nodes, pleura of right lung, mediastinum, pericardium, liver, and right kidney; hydrohemopericardium (1,300 cc.); hydrohemothorax, right (300 cc.); infarct of upper lobe of right lung; chronic passive congestion of liver and spleen.

Destructive Osseous Lesions in Early Syphilis*

Response Following Penicillin Therapy

ROBERT J. GLASER, M.D. and VIRGIL SCOTT, M.D.

ST. LOUIS, MISSOURI

DESTRUCTIVE lesions of the bones are a well authenticated but rare type of osseous involvement in early syphilis. Although other skeletal manifestations are not uncommon during this stage of the disease, Reynolds and Wasserman¹ were able to collect only fifteen cases of destructive bone lesions from the literature, prior to 1942. These authors reported an additional fifteen cases observed in a total of approximately 10,000 patients with early syphilis. Since their report Exley and Newton² and Lefkovits and Cross³ have each presented one case.

The favorable response of this type of lesion during weekly treatment with the arsenicals and bismuth has been demonstrated.¹ Under prolonged treatment methods, complete healing as determined by x-ray examination has occurred in periods ranging from four to ten months and in the few patients on whom follow-up data are available, the ultimate prognosis for cure with rare exceptions appears to be no less favorable than in the absence of this complication. With the demonstration of the therapeutic efficacy of penicillin in uncomplicated early syphilis, it becomes of importance to determine the effect of this anti-

biotic on rare manifestations of the disease such as this, and in addition, since it has not previously been studied, the effectiveness of an intensive regimen, wherein treatment is completed even before roentgenographic evidence of bone repair has begun.*

Penicillin has been employed in only one published case, that of Lefkovits and Cross.³ Although in their patient the initial response was satisfactory, the effect of treatment was complicated by the administration of two courses of penicillin (2.4 million units in 7.5 days, 4.0 million units in ten days) separated by an interval of approximately one month. Parenthetically, the indication for retreatment is not stated in the protocol. Since their patient was observed for only forty-eight days following the initial course of penicillin and healing was not complete at that time, the ultimate outcome was not determined.

CASE REPORT

N. P., (No. 129,849), a twenty-three year old white divorced female, reported to the Washington University Clinics on October 17, 1945, complaining of severe headache of six weeks' duration. On examination in the Otolaryn-

* No reports have appeared regarding the effectiveness of intensive arsenotherapy on this type of lesion.

* From the Departments of Internal Medicine and Preventive Medicine, Washington University School of Medicine, the Syphilis Clinic of the Washington University Clinics and the Barnes Hospital, St. Louis, Mo. The work described in this report was performed under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Washington University, and under a grant-in-aid from the National Institute of Health, United States Public Health Service.

gology Clinic, acute frontal sinusitis was suspected but was not confirmed by x-ray. Because the serologic test for syphilis was positive on routine examination, she was referred to the Syphilis Clinic at which time the diagnosis of early syphilis was established. The patient was admitted to the Barnes Hospital on November 8, 1945.

According to the patient serologic tests for syphilis had been negative on three previous occasions: ten years before her present admission, while hospitalized elsewhere for an appendectomy; one year before on premarital examination and four and one-half months previously on pre-employment testing. At the time of her marriage in October, 1944, her husband's premarital STS* was said also to have been negative. The marriage lasted six months; the patient obtained a divorce in March, 1945, nine months before her admission to the hospital. The husband's syphilitic status at the time of separation is not known, but the patient's allegedly negative STS four months later is presumptive evidence that he was not infected.

During the five months prior to entry the patient admitted repeated sexual exposure with a single consort. Two and one-half months before admission the latter developed a urethral discharge and was treated for gonorrhea elsewhere with penicillin.† At the same time the patient also received penicillin (three injections in one day), the diagnosis of a gonococcal infection apparently based on epidemiologic evidence.

Shortly prior to this time (about three and one-half months before admission) the patient struck her head in the left occipitoparietal region on a sharp ledge. A tender "knot" developed at the site; the lump persisted although tenderness disappeared in three days. After a symptom-free interlude of approximately six weeks, headaches characteristic of the present illness began two months before admission. These were predominately frontal in location, dull but intense and worse on movement of the head;

at times there was radiation posteriorly over the cranial vault. The characteristic feature of the headache was its nocturnal occurrence, the patient being awakened regularly at 4:00 A.M. At one time her right eyelid was said to have been swollen and discolored but these signs subsided spontaneously and were not apparent on admission. Approximately six weeks before admission the headache became bilateral and point tenderness developed on the left at the site of the previous injury. Simultaneously, three scattered skin lesions appeared. The patient denied any lesion, genital or extragenital, which in retrospect might have represented a chancre. There had been no bubo, generalized skin rash, oral lesions, sore throat or other bone pain.

On physical examination after admission to the hospital, the rectal temperature was 38.0°C., pulse 100 per minute, respirations 20 per minute, blood pressure 130 mm. Hg systolic and 70 diastolic. Three red, partially crusted papules were present on the skin; one each on the inner surface of the left arm, the right side of the neck and the medial aspect of the left mid-thigh. Over the region of the left occipitoparietal junction a small, exquisitely tender, hard mass measuring 1 by 2 cm. was easily palpable. This seemed attached to the skull but not to the overlying skin. No alopecia was evident and no other areas of tenderness or tumefaction were discovered, either over the skull or over the long bones. Examination of the eyes was not remarkable except for slight hyperemia of the optic discs. No lesions were visible on the mucous membranes of the oropharynx. The remainder of the physical examination was within normal limits. No adenopathy (regional or general) was present, no lesions or scars were visible on the external genitalia and the cervix appeared normal on inspection. The neck was not stiff and the neurologic examination was entirely negative.

Laboratory studies included a normal red blood cell count and hemoglobin. The leukocytes numbered 11,100; the differential showed 1 per cent juveniles, 4 per cent stabs, 52 per cent segmented forms and 43 per cent lymphocytes. The urinalysis was normal. On dark field examination of serum expressed from the papule

* Serologic test for syphilis.

† From the standpoint of syphilis this contact remained clinically and serologically negative on repeated examinations over a seven months period (November, 1945 to June, 1946).



FIG. 1. Lateral roentgenogram of skull before treatment. Three areas of bone destruction are visible in the parietal bone. A similar lesion is present in the frontal bone.

FIG. 2. Lesions show evidence of healing eighty-nine days following completion of penicillin therapy.

on the left arm, numerous *Treponema pallidum* were seen. Quantitative blood STS was reported as 120 Kahn units. Examination of the cerebrospinal fluid showed 15 lymphocytes, total protein 39 mg. per cent, colloidal test 0000000000 and a negative Kolmer complement fixation reaction with 0.5 cc. of spinal fluid. An ophthalmologic consultant recorded normal visual acuity and fields. The x-ray film of the skull showing multiple areas of destruction is reproduced in Figure 1. No abnormalities of the thoracic cage were evident on roentgenogram of the chest.

Hospital Course. Antisyphilitic treatment consisted of commercial sodium penicillin adminis-

tered by intramuscular injection in divided doses of 50,000 units every two hours day and night for ninety-six injections, a total of 4.8 million units in 7.5 days. No Herxheimer reaction (clinical or febrile) followed the institution of treatment. Within forty-eight hours bone pain and tenderness were strikingly improved and by the fifth day of treatment they had disappeared completely. The skin lesions healed rapidly. At the completion of treatment the quantitative blood STS was unchanged (120 KU); the cerebrospinal fluid contained two cells and was normal in other respects.

Follow-up Observations. Clinical and quantitative serologic examinations have been per-



FIG. 3. Further healing is apparent 122 days after penicillin therapy.

FIG. 4. Lesions are completely healed on the two-hundred eighth post-treatment day.

formed at approximately monthly intervals during the first post-treatment year and every three months thereafter. No recurrent infectious mucocutaneous lesions have been observed; the patient has remained symptomatically well during the one year and four months since treat-

TABLE I

SEROLOGIC RESPONSE FOLLOWING PENICILLIN THERAPY

Days After Treatment	Titer (Kahn Units)
1	120
29	40
50	4
64	4
70	3
92	4
120	2
166	2
215	0
236	1
271	1
295	1
341	1
474	0

ment. Quantitative blood serologic tests for syphilis in relation to days after the termination of penicillin therapy are shown in Table I. The cerebrospinal fluid on re-examination nine months following treatment was normal.

Periodic roentgenograms have been obtained since the completion of penicillin therapy. On the twenty-fourth post-treatment day there was as yet no change in the appearance of the lesions. As shown in Figure 2, evidence of healing had become apparent by the eighty-ninth day and at the end of 122 days (Fig. 3) there had been progressive improvement. On the next film (208 days) no residua of the destructive lesions remained. (Fig. 4.) The most recent x-ray examination of the skull, made 465 days after the completion of treatment, appeared normal.

COMMENTS

Although destructive osseous lesions are rare in early syphilis, other evidences of skeletal involvement (arthralgia, osteocopic pain and proliferative periostitis) are exceedingly common. For example, Wile and Sencar⁴ in a painstaking clinical study of 165 patients with early syphilis found symptoms and/or signs referable to the

bones and joints in sixty patients (36 per cent). The frequency of destructive lesions is not known since no one has reported the results of complete roentgenologic study on a series of patients with early syphilis. From the available reports, the sites of predilection appear to be the skull, the bones about the sternoclavicular joint and the long bones, in that order.

The diagnostic problem presented by these lesions has been repeatedly stressed^{1,3,5} and is re-emphasized by our own patient who in the six weeks prior to admission consulted three physicians and was accorded three different diagnoses—"sinusitis," "neuralgia" and "menopausal syndrome." It was only after an additional three weeks and six clinic visits to our own institution that the correct diagnosis was suspected and then only after the admission STS, routinely performed on all new patients, was reported positive.

In this patient the therapeutic response following penicillin therapy appears to have been as prompt as has been recorded during prolonged treatment with metal chemotherapeutic agents. Symptomatic relief occurred within forty-eight hours, striking and progressive improvement was apparent on follow-up x-ray examinations on the eighty-ninth and 122nd post-treatment days and all roentgenographic evidence of the lesions had disappeared before the 208th day (approximately seven months). The schedule employed in this patient (4.8 million units in 7.5 days) was one of the penicillin regimens assigned to this institution* for the routine treatment of patients with early syphilis. No additional penicillin was administered because of the presence of destructive bone involvement.

Although the relationship of the preceding blow on the head to the subsequent

* By the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council, the agency administering the nationwide cooperative study of penicillin in syphilis.

development of destructive lesions of the skull is conjectural, it is pertinent that Chesney, Turner and Halley⁶ have demonstrated the predisposing influence of trauma on cutaneous lesions of experimental syphilis in rabbits and have reported similar instances in early syphilis in man. Parenthetically, in late syphilis trauma is more frequently implicated as a factor predisposing to the development of lesions, osseous as well as cutaneous, e.g., in benign late (gummatous) syphilis.⁷

Whether the penicillin administered elsewhere shortly before onset of the present illness affected the course of syphilis in this patient is speculative. There is ample evidence both in man and in the experimental animal that penicillin in small doses administered during the incubation period of syphilis may modify or completely suppress the early manifestations of the disease.^{8,9} Although it was not possible to date the onset of syphilitic infection in this patient either by historical data or by epidemiologic investigation, it is conceivable that the small amount of penicillin administered for gonorrhea approximately two weeks before the onset of headache and four weeks before the appearance of three scattered skin lesions of the secondary type may have exerted a modifying and/or suppressing effect.

SUMMARY

A case report of destructive osseous lesions of the skull in early syphilis is presented. Penicillin therapy (4.8 million units in 7.5 days) afforded prompt symptomatic relief and complete healing of the involved areas within a seven month period. The results in this patient compare favorably with those reported during prolonged treatment with the arsenicals and bismuth.

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This Society was organized in the fall of 1946 by a representative group from various schools in the South who believe that enough good work is now being done below the Mason-Dixon Line to justify a regional organization.

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EXPERIMENTAL OBSERVATIONS ON THE PRODUCTION OF PERICARDIAL ADHESIONS AND ON LIGATION OF CORONARY ARTERIES IN RATS

ALEX W. BOONE, M.D. (*introduced by Joseph W. Beard, M.D.*)

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

Claude S. Beck and others have pioneered work indicating that temporary augmentation of the coronary circulation is possible by producing adhesions between the myocardium and pericardium. As yet, however, no satisfactory simple method of producing these adhesions has been evolved.

Experiments have been performed upon 227 rats to determine the efficiency of substances that might be injected into the pericardial sac and thereby furnish collateral extracoronary blood supply. Experiments have also been performed to determine the effect of adhesions upon the relative physical efficiency of the normal rat and of the rat subjected to ligation of the left coronary artery. Various concentrations of thirteen different detergents and six miscellaneous agents were placed in the pericardial sac of the rat. Five per cent monoethanolamine oleate proved to be the most efficacious and non-toxic of the agents tried, producing good vascular adhesions without complications. These adhesions did not affect the efficiency of normal rats. Ligation of the left coronary artery of normal rats diminished their physical efficiency. Production of adhesions soon after ligation of the left coronary artery had little beneficial effect.

EXPERIMENTAL AORTIC VALVULOTOMY

H. G. SMITHY, M.D. and EDWARD F. PARKER, M.D. (*introduced by William J. Darby, M.D.*)

From the Department of Surgery, Medical College of the State of South Carolina, Charleston, S. C.

In an effort to perfect a technical approach to the aortic valve, a series of dogs was studied with the view of developing a surgical procedure which might be applicable to young patients suffering from aortic stenosis.

The aortic valve has been successfully divided by a specially devised valvulotome which is passed into one of the aortic cusps through the

wall of the ascending aorta with the resultant production of aortic insufficiency. Technically, the procedure is complicated by hemorrhage from the aortic wound. Methods utilized in controlling the bleeding and in the production of the valvular lesion are discussed. Further studies are in progress relating to electrocardiographic changes, microscopic alterations of the aorta and the permanency of the valvular lesion.

MECHANISM OF EDEMA FORMATION IN THYROTOXIC HEART DISEASE

ARTHUR J. MERRILL, M.D. and (*by invitation*) WALTER H. CARGILL, M.D.

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We have previously presented evidence for a forward failure hypothesis of edema formation in congestive heart failure. Essentially this consists of a marked reduction in renal plasma flow, and filtration rate is independent of venous pressure levels and is closely related to inadequacy of cardiac output. The low filtration rate results in a reduction of the amount of salt and water presented to the tubules. Almost complete reabsorption by the tubules occurs with a net retention of salt and water and consequent edema formation. The cause of cardiac edema in patients with high cardiac outputs, as in thyrotoxicosis, has not been explained.

In thyrotoxicosis the cardiac output and basal metabolism rate were elevated concomitantly but the cardiac output was slightly higher after the patient became compensated than it was during severe failure.

The renal plasma flow in uncomplicated thyrotoxicosis followed no definite pattern but in the same patient tended to fall as the basal metabolism fell.

In seven patients with edema and orthopnea which were controlled easily, the renal plasma flow and filtration rate were normal or elevated. In all with a slightly diminished renal plasma flow, a supernormal level was found shortly after the patient became compensated. In one patient with moderate failure the renal plasma flow was decreased. In one patient with the most severe anasarca and ascites the renal plasma flow and filtration rate were quite low.

As the patient's thyrotoxicosis improved with propylthiouracil, first the filtration rate and finally the renal plasma flow became normal but the renal plasma flow was decreased. The latter increased as the patient's thyrotoxicosis improved with propylthiouracil.

Thus further evidence is found of a mechanism for reduction of the renal plasma flow and filtration rate when the cardiac output becomes inadequate for the metabolic needs of the tissues, even though the cardiac output may be well above the accepted average normal. When this vasoconstriction is extreme, the filtration rate and consequently salt and water filtration are reduced and edema occurs. One may surmise that the patients with less severe failure and normal renal studies at rest had inadequate cardiac outputs on exertion. We have shown that this will produce depression of the renal plasma flow and filtration rate in other types of heart failure and it is logical to suppose that a similar mechanism would operate here.

CHANGES IN RESPIRATORY EFFICIENCY AND DYNAMICS IN EXPERIMENTAL PULMONARY CONGESTION

HOWARD E. HEYER, M.D., JAMES HOLMAN,
M.D. and GEORGE T. SHIRES, M.D. (*intro-
duced by Morton F. Mason, M.D.*)

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Experimental pulmonary congestion and edema were produced in dogs by rapid venous infusion of saline and buffer solutions. Continuous determinations were made of tidal exchange, intrapleural pressure fluctuations, ventilation per minute and of jugular venous pressure. Eighteen animals were utilized in all. In several experiments comparative determinations were made at rest (nembutal anesthesia) as well as after the hyperpnea induced by rebreathing CO₂ and oxygen, or by experimental congestion. The rapid infusion produced marked pulmonary congestion and edema, confirmed by post-mortem examination. Generalized visceral congestion and progressive elevation of venous pressure to over 500 mm. of saline were noted in all experiments. Intrapleural pressures were below atmospheric levels prior to infusion, but with increasing congestion expiratory pressures

rose well above atmospheric levels in all cases. Inspiratory pressures either became more negative or shifted slightly toward atmospheric levels. Total intrapleural pressure changes increased markedly and mean intrapleural pressures deviated toward atmospheric levels. Carbon dioxide hyperpnea caused marked increases in total intrapleural pressure changes and an increase in the negative pressure developed during inspiration. In five of eight animals given CO₂, the expiratory intrapleural pressure remained below the atmospheric level, even with marked hyperpnea; in the remaining three animals it rose above this level.

The average tidal air increased markedly after CO₂ administration (often doubling), and the ventilation per minute rose even more sharply. During maximum pulmonary congestion tidal exchange decreased markedly, even with gross hyperpnea, while the ventilation was either slightly increased or decreased.

$$\frac{\text{Tidal exchange (cm.}^3\text{/meter}^2\text{)}}{\text{Total intrapleural pressure change}}$$

was utilized as an index of efficiency of respiration. This index rose abruptly after CO₂ administration and decreased sharply after pulmonary congestion was produced. Vagotomy slowed the respiratory rate, but did not abolish the shift in intrapleural pressure to levels above atmospheric, nor did it prevent the rapid decline in respiratory efficiency after congestion. Marked activity of expiratory muscle groups occurred with severe pulmonary congestion. Section of the cervical cord abolished these movements, but failed to cause expiratory intrapleural pressures to drop to subatmospheric levels in all cases. The authors conclude that hyperpnea produces increased efficiency of breathing in the normal lung, whereas the hyperpnea of pulmonary congestion is accompanied by a marked decrease in efficiency of respiration. The latter phenomenon is ascribed mainly to changes in the distensibility of pulmonary tissues. The shift in intrapleural pressure toward positive values (with congestion) is partially explainable by increased activity of expiratory muscles, but the failure of vagotomy and cord section to abolish these changes indicates that local changes in the lungs are also causative.

PULMONARY ARTERIAL PRESSURES IN CONGESTIVE FAILURE AND EMPHYSEMA

JOHN B. HICKAM, M.D. and WALTER H. CARGILL, M.D. (introduced by Eugene A. Stead, Jr., M.D.)

From the Duke University School of Medicine, Durham, N. C.

Many phenomena seen in diseases of the heart and lungs are commonly ascribed to elevation of pressure in the lesser circulation. Until recently, there have been few opportunities for determination of this pressure in man. The technic of intracardiac catheterization permits measurement of pressures within the pulmonary artery and simultaneous determination of the cardiac output by the Fick method. This technic has been applied to the study of the pulmonary circulation in patients with pulmonary emphysema, congestive heart failure, and mitral stenosis, conditions which have been thought to bring about an elevation of pressure in the lesser circulation.

Pulmonary arterial pressure and cardiac output were determined while subjects were at rest and while they were carrying out exercise sufficient approximately to double the resting oxygen consumption. In normal subjects the mean pulmonary arterial pressure at rest is of the order of 10 to 15 mm. of mercury and is substantially unchanged by increases in cardiac output up to nearly twice the resting level. Subjects with emphysema who have an elevated pulmonary pressure at rest show a further large increase in pressure when the cardiac output is raised by exercise. Subjects with congestive failure on the basis of hypertension or aortic regurgitation usually have a high resting pulmonary pressure. During exercise, the pulmonary pressure undergoes an additional large elevation, but the cardiac output is increased little or not at all. The results in subjects with advanced mitral stenosis resembled those seen in left ventricular failure.

The data indicate that the normal pulmonary vascular bed can accommodate considerable increase in blood flow over the resting level without a significant increase in pulmonary arterial pressure. The results in emphysema suggest a rigid vascular bed which responds with a sharp elevation of arterial pressure to an increase in cardiac output. The mechanism by

which the pulmonary pressure becomes elevated in cases of left ventricular failure is uncertain. It might possibly result from elevation of the left atrial pressure, constriction of pulmonary arterioles or development of edema within the lung. In mitral stenosis the failure of the cardiac output to rise in correspondence with the elevation of pulmonary pressure during exercise was unexpected.

USE OF TETRAETHYLAMMONIUM CHLORIDE IN THE TREATMENT OF EXPERIMENTAL ACUTE ARTERIAL INSUFFICIENCY

F. W. COOPER, JR., M.D. (introduced by Arthur J. Merrill, M.D.)

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

It has been proved conclusively by Leriche and his co-workers that sympathectomy will prevent massive gangrene and death following extensive arterial resections in animals. "The critical period" following arterial resection appears to be the optimal time for removal of constrictive arterial impulses which may inhibit the dilatation of collateral vessels.

A group of twenty animals weighing 9 to 15 Kg. was operated upon with the trifurcation of the aorta being excised distal to the inferior mesenteric artery. The deep circumflex iliac arteries, the two external iliac arteries and the common hypogastric trunk were excised. Ten of the animals were given tetraethylammonium chloride in the proportion of 25 mg. per Kg. of body weight as a sterile 10 per cent solution, intramuscularly. Similar doses were given every eight to twelve hours for three days.

In the control group nine of the animals died within one to five days with paralysis, discoloration and swelling of the posterior extremities. All of the animals treated with tetraethylammonium chloride survived except for one in which extensive cellulitis developed following injection of the drug through technical error in the posterior extremities. The animals so treated demonstrated a transient weakness and decreased functional tolerance for one to four days but returned to relatively normal activity at the end of this time.

The enlargement of the collateral channels about the site of aortic excision was demon-

strated by arteriography. Tetraethylammonium chloride may be a valuable adjunct in the treatment of acute arterial injuries.

PHLEBOGRAPHY FOR THE STUDY OF OBSTRUCTION OF THE VEINS OF THE SUPERIOR VENA CAVAL SYSTEM

SOL KATZ, M.D., HUGH HUDSON HUSSEY, M.D. and JAMES ROSS VEAL, M.D. (*introduced by Harold Jeghers, M.D.*)

From the Departments of Medicine and Surgery, Georgetown University School of Medicine, Georgetown Division of Medical and Surgical Division of Gallinger Municipal Hospital, Washington, D. C.

Phlebography is a precise method for study of lesions causing obstruction of the superior vena cava or its main tributaries, except the internal jugular vein which is inaccessible. Diodrast has usually been employed as the contrast medium. The external jugular vein is the preferred site of injection for visualization of obstruction of the superior vena cava or innominate vein; the median basilic vein, for the subclavian and axillary veins. The interpretation of phlebograms of the superior vena caval system is simple and errors are much less frequent than with phlebograms of the lower extremity. No other method, except anatomic dissection, affords as much information about the location and extent of collateral venous circulation.

Cases illustrative of obstruction of the superior vena caval system at various points are presented. It is emphasized that comparative measurements of the venous pressure are a valuable supplement to phlebography. They provide a more exact appraisal of the functional capacity of the collateral circulation than phlebographic study alone.

RELATION BETWEEN ARTERIAL PRESSURE AND BLOOD FLOW IN THE FOOT

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From the Departments of Medicine, Emory University, Atlanta, Ga., and Duke University School of Medicine, Durham, N. C.

The relationships between blood flow and arterial pressure in man have never been clearly elucidated. A satisfactory technic for raising and

lowering the arterial pressure in a part without using either vasoconstrictor drugs or intense sympathetic stimulation or causing venous congestion has been lacking. Because of its relatively large surface area, the foot offers an ideal for studying the relation between arterial pressure and blood flow in the skin. By standing upright the mean arterial pressure in the foot may be doubled. Venous congestion can be avoided by applying to the foot a pressure which exceeds the hydrostatic venous pressure but is well below the arterial diastolic pressure. On release of the external pressure, blood flows into the foot under a tremendous pressure head, which is unopposed on the venous side until the foot is filled. This seems to be a logical means of increasing the rate and amount of blood flowing into a foot with vascular disease; contrary to most current clinical procedures, it does not produce a deficit of blood flow for each gain, for the pressure required to empty the foot of its venous blood does not impede arterial inflow. The blood flow with the subject in the recumbent and standing positions is measured by means of a plethysmograph.

In a given subject the blood flow in the foot is related to: (1) Peripheral vascular resistance, which depends on (a) the amount of vasodilatation, (b) the amount of blood in the vessels which must be moved forward, and (2) the arterial pressure head. With the subject recumbent the blood flow in the foot is greatest when the foot is emptied of its venous blood and the vessels are maximally dilated by heat or previous arterial occlusion, for this situation offers the least peripheral vascular resistance. On standing, the blood flow is also greatest when the foot has previously been emptied of its venous blood.

On standing the mean arterial pressure in the foot is approximately doubled because of the added pressure exerted by the column of blood extending from the foot to the arch of the aorta. If the foot is emptied of its venous blood by external pressure, the increased pressure head is unopposed by residual blood in the foot and by the hydrostatic venous pressure provided the venous valves are competent.

The present study has shown the following: Motionless standing increased the blood flow in the foot two to four times above the recumbent level. The large increase in arterial pressure

was not sufficient to dilate maximally the vessels which still retained their tone but apparently sufficient to force more blood through these vessels than could be accounted for by a simple increase in pressure with no increase in vessel size. The blood flow in the erect position at a temperature of 32°C. was only one-fourth as large as when the vessels were maximally dilated by a temperature of 45°C. The blood flow erect at 32°C. was approximately equal to the blood flow supine at 45°C. Blood flow supine in the foot emptied of its venous blood was about 50 per cent greater than in the non-emptied foot.

These observations suggest that a properly timed peripheral venous pump rhythmically emptying the foot of its venous blood would cause at least a 100 per cent increase in the blood flow of the erect subject above that present in the same subject recumbent. The actual value of this procedure in the treatment of peripheral vascular disease remains to be evaluated.

DIRECT ACTION OF HYPOXIA UPON THE VASOMOTOR CENTER

THEODORE G. BERNTHAL, M.D. (*introduced by Paul F. Hahn, M.D.*)

From the Department of Physiology, Medical College of South Carolina, Charleston, S. C.

The responses of the vasomotor center (anesthetized dogs) to hypoxia were recorded during the absence of all known chemoreceptor support. Responses of the vasomotor center were indicated by changes in arterial blood volume flow in the foreleg. The vascular bed of the foreleg was protected from hypoxia and local hemodynamic conditions were maintained constant. Thus, changes in leg blood flow during hypoxia could result only from altered activity of the vasomotor center.

In four of eleven animals, reduction of the oxygen tension of inspired air to 0-52 mm. Hg caused only diminished leg blood flow, indicating predominance of excitatory action of hypoxia at the vasoconstrictor center. In six animals the responses were mixed, vasoconstriction occurred during some intensities of hypoxia or at some stage of single responses, vasodilatation at others. In one animal only vasodilatation occurred.

The results suggest two separate but simultaneous effects of hypoxia on the vasoconstrictor center, one depressant and one excitatory, with

a varying balance between them. In general, responses in which excitation dominated were the more frequently encountered. A corollary conclusion is that the arterial hypotension commonly exhibited during hypoxia by chemoceptively deafferented animals is not dependent upon depression of the vasoconstrictor center.

SOME CLINICAL EXPERIENCES WITH MEMBERS OF THE VITAMIN M GROUP (PTEROYLGLUTAMIC ACID, FERMENTATION FACTOR AND PTEROIC ACID)

EDGAR JONES, M.D. (*by invitation*), HENRY F. WARDEN, M.D. (*by invitation*) and WILLIAM J. DARBY, M.D.

From the Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.

Pteroylglutamic acid (PGA) is hemopoietically active when administered orally or parenterally to patients with sprue, pernicious anemia or nutritional macrocytic anemia. A comparison of its activity with liver extract indicates that orally administered PGA results in reticulocyte maxima equally as high as does liver extract. The subsequent erythrocyte regeneration is satisfactory. Eight patients who had been treated in a previous relapse with liver extract responded with equally good or higher erythrocyte levels when treated in a subsequent relapse with 5 to 15 mg. of PGA daily.

In sprue PGA can favorably influence the gastrointestinal malabsorption as reflected by the return toward normal of glucose tolerance, stool fat content, vitamin A tolerance, serum carotene and plasma tocopherol. The gastrointestinal picture as revealed by x-ray has reverted to normal in one patient under constant therapy with PGA. The effect of PGA on the neurologic defects in pernicious anemia remains to be clarified.

A case of sprue has exhibited a reticulocytosis of 38 per cent accompanied by clinical and hematologic improvement following daily parenteral administration of 10 mg. doses of "fermentation factor" (pteroyltriglutamic acid). A patient with pernicious anemia in relapse failed to respond significantly to the oral administration of 7.0 mg. daily of pterioic acid but subsequently responded to the oral administration of 5 mg. of PGA daily.

UREA SYNTHESIS IN THE NEPHRECTOMIZED RAT. A METHOD FOR THE STUDY OF RAPID CHANGES IN PROTEIN METABOLISM

FRANK L. ENGEL, M.D., E. IRENE PENTZ,
M.D. (*by invitation*) and MILDRED G.
ENGEL, M.D. (*by invitation*)

From the Department of Medicine, Emory University
School of Medicine, Atlanta, Ga.

There has been increasing interest during recent years in the relation of illness, injury and various endocrines to nitrogen metabolism. Much has been learned about overall nitrogen balance but there are many gaps in our knowledge of the protein metabolism and the exact time relationship between various types of stimuli and the responses in acceleration or inhibition of protein catabolism.

The present report presents an improved method for the study of rapid changes in protein metabolism in rats by which one is enabled to detect changes in three hours or less with a high degree of accuracy. It is based on the measurement of urea nitrogen accumulation in nephrectomized rats. Its validity depends on (1) the availability of an accurate and sensitive method for the determination of blood urea, (2) the equal distribution of urea throughout the total body water, (3) experimental periods short enough so that significant changes in body water composition are unlikely and (4) a relatively constant rate of rise of blood urea nitrogen during a reasonable period after nephrectomy. These criteria have been met. Data will be presented analyzing the method, and some experiences with the use of various amino acid mixtures, adrenal cortical extract and the effects of hemorrhages and shock will be considered.

PLASMA PROTEINS IN CONTROL AND INJURED DOGS, GOATS AND RATS

ALFRED CHANUTIN, M.D.

From the Biochemical Laboratory, University of
Virginia, Charlottesville, Va.
(This work was done under contract with the Medical
Division, C.W.S.)

This laboratory has been engaged in the fractionation of serum of control and injured animals. The serum and fractions have been studied by electrophoretic and chemical procedures.

The serum of dogs injured by mustard, heat, cold or turpentine injections showed increases in alpha and beta globulins and a decrease in albumin concentrations. Fractions isolated from these sera were not present in the serum of control animals and some were characterized by a high lipide content.

The electrophoretic changes in the serum of goats injured by mustard or turpentine were characterized by an increase in the beta globulins and a decrease in albumin concentrations. No increase in lipoproteins was demonstrated in the goat. Four electrophoretically pure proteins have been isolated.

The proteins of whole plasma of rats showed comparatively little change electrophoretically until they were separated into four fractions. After injury, marked increases were noted in the alpha and beta globulins and a decrease in albumin concentrations.

URINE VOLUME AND URINARY SODIUM EXCRETION DURING WATER DIURESIS

A. J. CRUTCHFIELD, M.D. (*by invitation*)
and J. EDWIN WOOD, JR., M.D.

From the Department of Medicine, University of
Virginia Medical School, Charlottesville, Va.

The influence of water diuresis on urinary sodium excretion has been observed in normal individuals and patients with congestive heart failure. Hourly total renal excretion of sodium and urine has been determined for six consecutive hours following the ingestion of one liter of water. This pattern of sodium and water excretion was studied following: (1) plain water and (2) plain water plus certain diuretic substances, appropriately preceded in each case by plain water controls. Sodium determinations were made by the photometric method, the accuracy of which has been discussed in a previously submitted summary. Altogether eighty-six experiments have been done on forty patients.

From these experiments a definite pattern of sodium and water excretion has been recorded. This pattern is essentially the same in outline for both normal and congestive heart failure patients, though quantitatively different.

Mercupurine and intravenous aminophyllin regularly produced a disproportionate increase

in urine volume and total urinary sodium in favor of the latter. This suggests that the primary renal action of these substances may be depression of tubular reabsorption of sodium. Xanthines by mouth have a similar, though much less powerful effect. Urea and glucose under the conditions of this experiment produced no significant effect on urine volume or sodium excretion.

From these observations it would appear that water diuresis does not increase urinary sodium elimination but may actually depress it.

FLUORESCENT TRACER SUBSTANCES IN THE DETERMINATION OF CIRCULATION TIMES IN MAN

WILLIAM ADOLPH, M.D., TRAVIS WINSOR, M.D., WALTER C. RALSTON, M.D. and GEORGE M. LEIBY, M.D. (*introduced by George E. Burch, M.D.*)

From the Medical Division, Birmingham General Hospital, Van Nuys, Calif.

The purpose of the present presentation is (1) to demonstrate the use of riboflavin as a fluorescent tracer substance, (2) to present a technic which renders circulation time of greater clinical value and (3) to demonstrate the value of measurements in various segments of the cardiovascular system. The technic was to raise a histamine wheal on various portions of the body. After approximately one minute riboflavin was injected into the antecubital vein. The time was measured from the beginning of the injection to the appearance of yellow-green fluorescence in the periphery of the wheal detected using filtered ultraviolet light. Normal individuals and patients with congestive failure were studied. A number of fluorescent materials were studied *in vivo* and *in vitro*. Riboflavin and fluorescein were the most innocuous, were readily diffusible in tissue spaces and easily visible giving sharp end points in a darkened room. Peak fluorescence for riboflavin occurred in dilutions ten times greater than for fluorescein. Maximum fluorescence was more intense with fluorescein. Optimum dose for riboflavin *in vivo* was 0.8 mg. per kilo. Arm to arm times were determined

among normal individuals using riboflavin and fluorescein. Both substances gave comparable results (range fourteen to twenty-six seconds, average 19). Riboflavin circulation times varied with age, the shortest normal arm to arm time being six seconds in an infant. Circulation times were determined over short (arm to arm) and long (arm to foot) segments of the vascular tree among normal individuals and those with congestive failure. Times obtained from long segments were a more sensitive index of circulatory retardation than times obtained over shorter segments. Circulation times through a systemic arterial segment was determined by taking the difference between arm to arm and arm to foot times. In some instances the segment time was abnormal (greater than twelve seconds under standard conditions) in patients with failure when the arm to arm time was normal.

OBSERVATIONS ON ABDOMINAL VISCERAL PAIN PATHWAYS IN PATIENTS UNDERGOING CELIAC GANGLIONECTOMY AND VAGOTOMY OR SYMPATHECTOMY

KEITH S. GRIMSON, M.D.

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

Celiac ganglionectomy alone has been performed during the course of exploratory laparotomy in four patients with so-called biliary dyskinesia. Another had right splanchnicectomy only. Celiac ganglionectomy was employed for pain from recurring pancreatitis in one patient. Celiac ganglionectomy and subdiaphragmatic vagotomy were performed in two patients with severe functional abdominal pain. Observations concerning the effect of these operations and also concerning visceral pain after transthoracic vagotomy for peptic ulcer and after splanchnicectomy during sympathectomy for hypertension will be presented.

It is concluded that the vagus nerves do not carry visceral afferent pain pathways and that the splanchnic nerves do. A major portion of the splanchnic visceral afferent pain pathways travel through the celiac ganglia.

Editorial

Allergy Comes of Age

WHEN discoveries in science open up new avenues of approach to old problems in unrelated as well as in related fields, the usual tendency is to hurriedly attempt application if there is any suggestion of practicability, to build on theories as though they were fact, to stress the particular technics employed and to enlarge the vocabulary with newly coined words of limited and special significance. This frequently leads to an unfortunate isolation of the subject, which suffers at the hands of enthusiasts until further study and wiser minds develop the germ of truth, if there be any, and discover that the underlying principles based on fact actually are in harmony with those in other fields and that the new principles complement rather than oppose the old or exist independently of them. Of no field is this more true than of allergy which was opened up as the direct result of the discovery of anaphylaxis, in its turn a by-product of von Behring's diphtheria antitoxic serum therapy.

Not many years ago allergy was the neglected stepchild of the medical profession. To most physicians allergy merely indicated a few common but not vitally important diseases—hay fever, asthma, urticaria—and the allergist was regarded merely as a technician who did skin tests, the more extensive the better, which he assumed were a sort of diagnostic Rosetta stone. Unfortunately, this too frequently was warranted.

Gradually but steadily the situation for allergy has improved. It is emerging from its adolescence, a period quite common to

most new fields of science, because careful study on the part of many has brought new knowledge which evidences the basic soundness of its concepts. Today allergy stands at the threshold of real development, for the broader vision of many minds has served to extend its horizons and increase its applicability to the possible solution of many medical problems.

It is interesting to note the extent in recent years to which allergy has come to engage the attention of those in the basic sciences of medicine, biochemistry, immunology and immunochemistry, pathology and pharmacology, as well as those immediately concerned with clinical problems, the internist, the pediatrician and others engaged in specialty fields. As proof that this is so, one need only read the contributions in this symposium dealing with pathology, immunochemistry, applied immunology and pharmacology, as well as those which concern themselves with such clinical phases as the important drug allergies, allergic dermatitis and the neuropathies, asthma and the relation of the psychic to the somatic manifestations of allergic disease. Allergy has shed its swaddling clothes and its immaturity and must be reckoned with.

A question of more than minor concern is, what are the medical schools doing for the undergraduate, and the hospitals for their interns and residents, in a field which requires their attention but to which they have had little or no introduction? A recent survey of undergraduate allergy instruction in

Class A medical schools in the United States shows a rather deplorable lack of facilities, perhaps it would be more accurate to say a failure to utilize existing opportunities for teaching the principles of allergy and providing a degree of clinical experience for the medical student. The responsibility for this must rest with the heads of departments who either fail to grasp the significance of allergy in relation to medicine, and this is certainly true of some, or, as is more probable, who cannot find time for an organized course in an already crowded schedule. That something should be done is evidenced by the complete unfamiliarity of recently graduated physicians, interns and general practitioners with the rudiments of a subject which they are promptly called upon to use.

Anyone cognizant of the recent developments in allergy and the increasing applicability of the concepts of allergy to problems in internal medicine and pediatrics must admit that it is an integral part of the basic medical sciences, bacteriology, immunology, pathology, pharmacology, physiology and clinical medicine. Bacteriology cannot be taught as it was a generation ago without reference to the tuberculin-type response of man to bacterial substances, the implications of this response, and the general relation of sensitivity to immunity. The course in immunology would be sterile without a consideration of experimental sensitization and such special technics as passive transfer, the Schultz-Dale and precipitin tests and transfer to normal human skin; this leads naturally to consideration of artificial sensitization of man to heterologous serum, serum disease and the subsequent allergic state which may be recognized by cutaneous and ophthalmic tests. In pathology the histologic responses are not to be understood without consideration of the underlying reasons for such tissue changes as the Aschoff bodies, periarteritis and fibrinoid degeneration, all of which introduce allergy as one of the possible factors in human diseases. Pharmacology cannot be adequately

taught without inclusion of the increasingly important subjects of drug allergies and the antihistaminic drugs and the reasons why they have come into being.

So it is throughout all the basic courses, the fundamentals of allergy are part and parcel of them, and but little time is required to point out their future clinical applicability so that the student may approach his clinical years well grounded in the principles of allergy. A few lectures, three or four, early in the third year would then suffice to coordinate the theories and facts with such diseases as are considered in whole or in part to be based on sensitivity; for example, rheumatic fever, tuberculosis, syphilis, the erythema group, periarteritis, disseminated lupus and many of the dermatoses, as well as the recognized diseases of allergy—asthma, serum disease, urticaria, angio-edema and the various allergic reactions to drugs.

Graduate education will automatically improve as undergraduate instruction such as outlined is adopted and as approved residencies in allergy are made more available. With regard to the latter one point should be emphasized, namely, that no resident in allergy or in any other subspecialty and restricted field should be accepted until the basic requirements in medicine or pediatrics have been fulfilled.

In all such rapidly expanding subjects as allergy it is necessary from time to time to pause and evaluate what has been accomplished. This symposium is an attempt to do just that, to take inventory of the present information in certain of the basic sciences and specialties of clinical medicine in which allergy appears to be a factor. It is the hope of the guest editors that these contributions will serve a useful purpose in furthering education in the realm of postgraduate medicine, which is one of the aims to which the American Journal of Medicine has dedicated itself.

ROBERT A. COOKE, M.D.

Classification of the Histologic Reactions in Allergic Diseases^{*}

MILTON G. BOHRD, M.D.

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HISTOLOGIC changes have been described in practically every clinical and experimental state known or thought to be allergic. Whenever similar changes have been noted in diseases of unknown origin or uncertain nature, the allergic mechanism has been invoked as a possible factor; and indeed, with this as a clue, evidence of other sorts has, in some of these states, piled up to support such explanations. Implicit in this type of research and reasoning is the question of the pathognomoncity of the morphologic changes seen in allergic inflammations. It is probable, and some of the evidence to support this will be presented below, that none of the histologic lesions in allergic states can be said to be pathognomonic although several of them are highly characteristic.¹

A second morphologic problem of considerable theoretic interest and some practical value is the classification of the numerous different lesions which have been described in allergic conditions. Classifications are notoriously subject to violent controversies which usually arise out of a misunderstanding of the nature of classification; it may therefore be well to look into just what one does when he classifies anything. *A classification is an arrangement of objects or phenomena according to a point of view.* Usually it is possible to arrange the same objects according to more than one point of view and at times one may choose from an extremely large number of viewpoints. Each of these classifications is as tenable

as any of the others. For classifications cannot be "right" or "wrong"; they can only be useful or not useful. Even "good" or "bad" can be applied to them only in relation to this usefulness.

Classifications may themselves be classified. For instance, they may be grouped according to the tools employed and the methods used by the classifiers. Thus, when anatomic change is the basis, we have a pathologic classification; and when clinical signs and symptoms are employed, we have a clinical classification. Such classifications, limited to a rather narrow point of view, may be of great value for purely descriptive purposes and are often necessary first approximations to more valuable classifications. It is when a classification according to one point of view correlates with classifications according to other viewpoints that the greatest usefulness is attained.

A purely histologic classification of allergic states would be of some value, it is true, but certainly not of much clinical value. The classification herein attempted, however, shows interesting relationships to clinical and immunologic data and it is probable, therefore, that the histologic pictures observed are related to the clinical and immunologic phenomena. The reader should be warned, however, that this classification is not a division into perfect, mutually exclusive groups. The position in the scheme of several of the conditions is uncertain; others seems to belong in two categories and many, alas, are mixtures of

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several. This classification is at best, then, tentative and will no doubt require frequent revision.

PATHOGENESIS OF AN INFLAMMATION

The allergic reaction results in injury to the tissues which is followed by that wide variety of changes subsumed under the general title of "inflammatory reactions." A consideration of the elements which determine the anatomic changes seen in inflammation will serve as one basis for classification and it will also make it easier to understand why, in all probability, no pathognomonic allergic reaction can be found. Traditionally, two important factors are recognized: (1) The strength of the inflammatory stimulus and (2) the responsiveness of the host; or in Osler's parable, the "seed" and the "soil." But this is not the whole story. There are two additional factors which greatly influence the anatomy of an inflammatory lesion, namely, (3) the rate at which the reaction develops or its *velocity* and (4) the time during which it is active or its *duration*. These additional factors are influenced, it is true, by the first two and are in part the result of the interaction between stimulus and reactivity; but, however they are produced, they determine the anatomy of an inflammatory lesion. This fact has rarely been stipulated but has long been tacitly implied in such well known designations as *acute*, *subacute* and *chronic*. Beyond these, the hemorrhagic or necrotizing character of *hyper-acute* inflammations is well known.

A minimum time is necessary before an injury can produce anatomic changes detectable by presently available methods. Death may ensue so rapidly, either because the stimulus is very strong or because the reactivity of the subject is so violent, that no anatomic changes are demonstrable; or the duration of the stimulus and the response may be so brief and restitution to normal so rapid that, again, no anatomic changes may as yet have been found.

Sudden death without significant anatomic changes may occur when the exciting stimu-

lus is apparently minor or at least with stimuli which in the great majority of persons and animals produce little or no damage. Such deaths are seen in the misnamed "status thymico-lymphaticus," in the fortunately rare hyper-reaction to small doses of drugs or after mental trauma.* Similarly, the anatomic changes observed in sudden death in anaphylactic shock are minimal, not in themselves sufficient to explain death and certainly not, in spite of repeated claims to the contrary, distinctive enough for a purely anatomic diagnosis. Certain other instances of sudden death without apparent adequate cause may be allergic.² In all of these, and in other similar instances, the characteristic feature is the marked hyper-responsiveness of the subject and I have proposed calling the phenomenon "Sudden Death in the Hyper-reactor State."

The number of elementary morphologic changes which enter into the anatomy of an inflammatory reaction is limited. They fall into four groups: (1) evidence of injury, (2) exudation, (3) proliferation and (4) repair.

Evidences of injury include necrosis and the accumulation of abnormal substances in cells (degeneration). They may be very slight or, as in necrotizing inflammation, they may dominate the entire picture. Exudation is the accumulation of substances from the circulating blood or lymph in the region of inflammation. To a large degree the severity of an inflammatory reaction is indicated by the complexity of the substances which accumulate (serum, plasma, leukocytes, erythrocytes); and inflammations are often classified according to the dominant element of the exudation (serous, fibrinous, purulent, hemorrhagic). Proliferation of cells, either of those originally present in the area of inflammation or of those reaching the area from the blood stream, may lead to the most characteristic

* I can well believe that it may be difficult to conceive of sudden death after mental trauma. I, too, might not believe in its existence if I had not myself seen such a case and performed the necropsy.

of all the features of "specific" inflammations. Repair is, of course, an element of all inflammations which regress but in some it characteristically accompanies the elements of active inflammation.

It seems probable, as a result of the last

cellular phenomena which follow are orderly and depend upon the kinds and amounts of the substances elaborated. The identity of the principal substance which is produced by tissue damage and which initiates the inflammatory sequence is still disputed.

TABLE I
DISEASES OF ALLERGIC AND POSSIBLY ALLERGIC ORIGIN*

Classification of Histologic Lesions	Diseases almost Certainly Allergic	Diseases Which May Have Allergic or Non-allergic Causes	Diseases in Which Allergy has been Suggested but Evidence is Inadequate
NECROTIZING: Tissue Selective	Arthus phenomenon Shwartzman phenomenon "Carbuncle" of kidney Diffuse cortical necrosis of kidney	Drug sensitivity Acute yellow atrophy of liver Acute pancreatic necrosis Necrotizing cholecystitis Necrotizing appendicitis	Encephalomyelitis ^{41,42} Demyelinating diseases ⁴³
Cell Selective		Thrombocytopenic purpura Granulocytopenia Aplastic anemia	
ANAPHYLACTOID:	Anaphylaxis Serum sickness Asthma Atopic dermatitis Pneumonia caseosa (tuberculous) Rheumatic pneumonia ⁴⁴	Sudden death in the hyper-reactor state Periarteritis nodosa Glomerulonephritis ⁴⁵	Disseminated lupus erythematosus Scleroderma Dermatomyositis Thrombo-angitis obliterans ^{46,47} Temporal arteritis ⁴⁸ Loeffler's syndrome ⁴⁹ Eosinophilic granuloma of bone Reiter's disease ⁵⁰
GRANULOMATOUS: Tuberculoid	Tuberculosis Brucellosis Tularemia Sporotrichosis Coccidioidomycosis		Histoplasmosis
Rheumatoid	Rheumatic fever Rheumatoid arthritis "Giant-cell" rheumatoid granulomas Rheumatoid scleritis Sympathetic ophthalmia ^{51,52}		

* References to literature only in those diseases not mentioned in the body of the paper.

ten years' investigation into the chemistry and physiology of the inflammatory reaction,³ that the initial impulse for the tissue changes is derived from substances released by the action of the injurious agent upon tissue cells, that these substances have very specific chemical structures (some of them have even been crystallized) and that the

Some believe it to be histamine or a "histamine-like substance." Menkin³ claims it is different from histamine and has named it leukotaxine.

The relevance of these concepts for allergic inflammation must be immediately apparent, regardless of whether histamine is the substance concerned or whether the

antigen-antibody reaction injures tissue and elaborates leukotaxine.⁴ There is certainly little in such ideas concerning the pathogenesis of allergic inflammation to lead to the expectation that the histology of a lesion so produced will always differ from other

ously my own notions of how the diseases fit into such a scheme and considerable disagreement will be found in this respect. Several important clinical and immunologic correlations are immediately apparent. The necrotizing and the exudative

TABLE II
CORRELATION BETWEEN HISTOLOGIC CLASSES AND CLINICAL AND IMMUNOLOGIC PHENOMENA IN ALLERGIC DISEASES

	Type of Clinical Reaction	Clinical Course (Velocity)	Duration	Skin Reaction	Antibody in Serum	Specific Infection	Eosino- philia	Necrosis
NECROTIZING	Immediate	Rapid	Short	0 or + Necrosis	0 or +	0 or +	0 or +	++++ (Diffuse)
ANAPHYLACTOID:	Immediate	Rapid	Short to moderate	Wheal type	Frequently +	0	+ to ++++	+ (Fibrinoid)
GRANULOMATOUS: Tuberculoid	Delayed	Variable	Short to long	Tubercu- lin type	0	+	0	++ (Caseous)
Rheumatoid	Delayed	Slow	Long	0	0	0	0 or +	++ (Fibrinoid)

non-allergic inflammations. What is apparently characteristic of allergic inflammations is their velocity and duration and similar lesions may be the result of other than allergic stimuli if the velocity and duration are the same.

A CLASSIFICATION OF HISTOLOGIC LESIONS
IN ALLERGY

- I. Necrotizing
 - (a) Organ-selective
 - (b) Cell-selective
- II. Anaphylactoid (exudative)
- III. Granulomatous
 - (a) Tuberculoid
 - (b) Rheumatoid

Table I lists the clinical entities which seem to fit into the above classifications, divided into three groups: Those which are almost certainly allergic, those which are sometimes allergic but may have other causes and those which have histologic similarity to allergic lesions and for which an allergic mechanism has been claimed but with no good clinical or immunologic evidence for such claims. These are obvi-

(anaphylactoid) lesions include all those conditions which clinically fall into the "immediate" reactions, the granulomatous lesions those which are the "delayed" reactions.⁵ Not all instances which fall into the first two groups have positive skin reactions but, when such reactions occur, they are almost always of the wheal type. All the lesions of the tuberculoid granulomatous type have positive skin tests but they are of the tuberculin type. The rheumatoid group has no characteristic skin reaction. Circulating antibodies have not been identified in all instances in any of the subdivisions but almost all in which they have been identified fall into the anaphylactoid group, a very few in the necrotizing and none in the granulomatous.* There are differences in the necrosis in tuberculoid and rheumatoid reactions; there is also the striking fact that in the first of these a living agent (bacterium, fungus, or virus) is identifiable and

* Under very special conditions circulating antibody may be detected in tuberculosis.⁶ Fundamentally, there may be no immunologic difference but for clinical purposes the difference is important.

in the second group no single organism has been implicated.

Thus it can be seen that the classification of allergic lesions according to histology has clinical and immunologic implications. These are summarized in Table II.

NECROTIZING LESIONS

Necrosis is present in some degree, usually slight or moderate, in almost all of the histologic lesions of allergy. In certain of them, however, necrosis dominates the whole picture or may even be the sole anatomic feature. The Arthus and Schwartzman phenomena of experimental allergy are such lesions and they have their counterpart in human disease.

Anatomically, the lesions are characterized by diffuse necrosis involving parenchymal cells, interstitial tissue, vascular structures and anything else in the area. (Fig. 1.) There is often a sharp boundary between areas of necrosis and normal tissue and one can imagine that the limits of the necrosis are determined by the diffusion of an antigen in a sensitized subject. Nuclear debris may be a striking feature in the necrotic zone. Around the area there is a variable amount of infiltration with inflammatory cells, usually neutrophil leukocytes. Eosinophilia is rare. In very rapidly fatal cases the peripheral cellular reaction may be entirely absent.

Several human pathologic states probably fall into this group of allergic necrotizing inflammations. Characteristic examples are the closely related conditions known as renal carbuncle and diffuse cortical necrosis of the kidney. Characteristically, these are preceded by renal infection of some kind (local sensitization) followed by a very sudden widespread necrosis of renal substance. Characteristically, too, this condition occurs as the result principally of two kinds of renal infections: Most of them are staphylococcal in origin and the remainder are usually due to pyocyaneus infections. Both of these organisms, it will be noted, produce soluble toxins.

Similar clinical and pathologic pictures of sudden onset, diffuse necrotization and little or no inflammation at the onset are seen in a variety of fairly common diseases which from time to time have been said to be allergic in origin. It is probable that the antigen-antibody reaction plays a part in some instances of these diseases but that they can be elicited by mechanisms other than the allergic reaction. Among the conditions claimed to be related to the Arthus or Schwartzman phenomena are acute pancreatic necrosis,⁷ necrotizing inflammation of the appendix,⁸ acute gangrenous cholecystitis and, above all, various types of drug hypersensitization. It has been claimed, for instance, that the sensitization to cinchophen is an example of the Arthus phenomenon.⁹

Now, it is here particularly, where drug hypersensitivity is being considered, that it is possible to see clearly the non-pathognomonic character of these lesions. Obviously, in cinchophen and other such hypersensitivities we are dealing with minute quantities of drugs to which most people exhibit no sensitivity and there are other evidences for the assumption of an allergic mechanism.⁹ Exactly similar lesions, however, can be produced by other drugs without any evidence of previous sensitivity. Thus, the necrosis of the liver, which is thought to be an Arthus phenomenon in cinchophen poisoning, is certainly a primary degeneration in chloroform, mushroom, arsenic or phosphorous poisoning. Primary necrosis of tissues may also result from vitamin deficiencies.⁴⁰

A phenomenon worthy of note in considering necrotizing inflammations due to drugs is organ specificity. Thus, cinchophen affects the liver but only rarely other organs, such as the pancreas.¹¹ Organ selectivity is, of course, even better known with primary destruction by chemical substances.¹⁰

The specificity of a chemical substance, however, may not be for a large organ but for a particular type of cell. Thus, following the use of gold, arsphenamine and especially sedormid,¹² many cases of thrombo-

cytopenic purpura were reported. The question of hypersensitivity in such instances and the relation of this hypersensitive state to a possible antigen-antibody reaction may be disregarded at this point in the discussion. It is important to remember, however, that similar destruction of blood platelets and production of purpuric states is well known as a result of protein hypersensitization and the antigen-antibody reaction.¹³ Similarly, leukopenic states may be the result of either drug hypersensitivity or protein hypersensitivity. Although in these conditions no actual necrosis may be demonstrated histologically, it is assumed that the antigen-antibody reaction destroys the individual cells wherever they occur or at their site of origin. In favor of this view is the recently reported experimental work of Squier and Lee¹⁴ who were actually able to demonstrate the progressive destruction of leukocytes *in vitro*. The high degree of antigen-antibody selectivity and specificity is well known in the allergic states but the high degree of organ or even cytologic specificity of these reactions requires much more study.

ANAPHYLACTOID ALLERGIC LESIONS

This group of lesions is characterized clinically by quick onset, relatively short course and often equally rapid regression, that is, by the "immediate" reactions of allergy. It is characterized pathologically by predominantly exudative changes: edema, swelling of collagen fibrils and in some cases degeneration and fibrinoid necrosis of collagen. The diseases which make up the bulk of an allergist's practice fall into this group as well as some interesting conditions whose position as allergic is equivocal.

Many of the anaphylactoid lesions are at a *presto* tempo, sudden in onset and short in duration. There is not time for anatomic change other than edema and the tissues are soon restored to a normal state. The edema may be seen grossly but in cases of acute edema it may not easily be demonstrable under the microscope since the technical methods employed by the his-

tologist, such as fixation, sectioning and especially dehydration, cause the tissues to shrink and revert to their pre-edematous appearance. It must be noted that this histologic simplicity has no relation to clinical severity; for in these edematous lesions one may include both simple urticaria on the one hand and fatal angioneurotic edema and anaphylaxis on the other, in all of which the anatomic findings are simply those of increased fluid at the site of the lesion.

A relatively simple lesion of this group (allergic coryza) is illustrated in Figure 2. The lesion is not fresh for the edema is chronic and the tissues did not shrink in the dehydrating process but essentially the lesion presents only edema, with a few inflammatory cells, some of them eosinophil leukocytes.

If the allergic insult be repeated often enough, restitution may not be entirely to normal and anatomic changes may be encountered which are the beginning of the *secondary* phenomena observed in allergic states. Here, no doubt, is the explanation for such frequently described lesions as "hypertrophy of muscles and vessel walls," "thickening of basement membrane" and others. Many of the changes in the skin of allergic dermatoses are secondary and non-specific.

The cellular exudation varies in degree and kind. Thus, in very acute lesions the only cells present may be neutrophil leukocytes and these may be very numerous. In other more chronic lesions large phagocytic cells, i.e., monocytes or histiocytes, may be numerous or even predominate.

There is a tendency for all of these lesions, from the most acute to the most chronic, to contain a number of eosinophil leukocytes. So common is this phenomenon that eosinophilia has perhaps been over-emphasized in the diagnosis of allergic histologic lesions; and the presence of eosinophilia has, from time to time led to the suspicion, for no other reason than the eosinophilia itself, that the disease may be allergic. For example, eosinophilic granu-

loma of the bone has recently been considered as possibly allergic in origin.¹⁵

I have discussed elsewhere at some length¹ the problem of eosinophilia in allergic and non-allergic diseases and will therefore limit this discussion to a statement of conclusions. Tissue eosinophilia is a highly characteristic finding in allergic lesions of the anaphylactoid type but it is not pathognomonic. It is highly characteristic for some non-allergic states (Hodgkin's disease, for instance) and is common in a wide variety of lesions. Furthermore, the absence of eosinophilia from a lesion does not necessarily mean that it is not allergic.

The necrosis which occurs in anaphylactoid lesions differs from that of both the predominantly necrotizing and the granulomatous lesions. In most instances it affects collagen and exhibits staining reactions resembling that of fibrin, hence *fibrinoid necrosis*. The distribution is focal and the foci are usually small and sharply delimited. Thus, in periarteritis nodosa (Fig. 3) only a segment of the wall of an arteriole may be involved while the remainder of the wall is intact.

Fibrinoid necrosis is a characteristic finding in periarteritis nodosa, so much so that one of the many synonyms of the disease is "necrotizing arteritis." The evidence is good that periarteritis nodosa may be the result of allergic mechanisms.¹⁶ It is almost inevitable, therefore, that other diseases which exhibit fibrinoid necrosis should be considered as possibly allergic. Thus, disseminated lupus erythematosus and dermatomyositis, both of which are collagen diseases¹⁷ with marked fibrinoid changes and both of which may be associated with periarteritis nodosa-like lesions,¹⁸ have been considered allergic. There is no conclusive evidence that the allergic mechanism operates in these conditions, although it is entirely possible that allergy may be responsible in some instances.

Brief consideration must be given to periarteritis nodosa. The study of this disease has stimulated renewed interest in allergic mechanisms in a variety of conditions and

especially in rheumatic fever and rheumatoid arthritis. Furthermore, the elucidation of the mechanisms by which it may be produced might mean that we shall have to re-evaluate certain therapeutic procedures such as serum therapy and the use of sulfonamides. The original idea that periarteritis nodosa might be allergic was based on pathologic studies¹⁹ but the most important work has been that of Rich and his associates¹⁶ who produced the disease by the injection of relatively large doses of foreign serum. Later²⁰ a relation to sulfonamide drugs was noted. Association with disease of undisputed allergic nature was found in not a few cases, especially with asthma.^{21,22} Recently, association with granulomatous lesions has been reported.²³ Necrotizing arteritis has been seen in glomerulonephritis, in tuberculous meningitis²⁴ and, as noted above, in disseminated lupus erythematosus and in dermatomyositis. Exactly similar lesions have been produced with hormones,^{25,26} carcinogens and in other ways which probably are not allergic.

Two solutions are possible for the relationship between periarteritis nodosa and allergy: The first is to accept the allergic theory and to say that all of the reported lesions are not "true" periarteritis nodosa but only resemble it. But in the absence of unequivocal etiologic criteria and with so variable and protean a clinical picture, anatomic criteria are the only criteria which can be depended upon to decide what constitutes periarteritis nodosa. For this reason the second solution seems to be the better one, namely, that anything which *looks like* periarteritis nodosa is periarteritis nodosa and that this condition has several perhaps many causes, one of which is allergy. This way of looking at the matter has the further advantage of the possibility of there being a common factor in all these states inclusive of allergy. One very interesting one has already been proposed by Selye²⁷ under the designation, "adaptation syndrome" and the "diseases of adaptation."

Rich²⁸ and others²⁹ have presented good

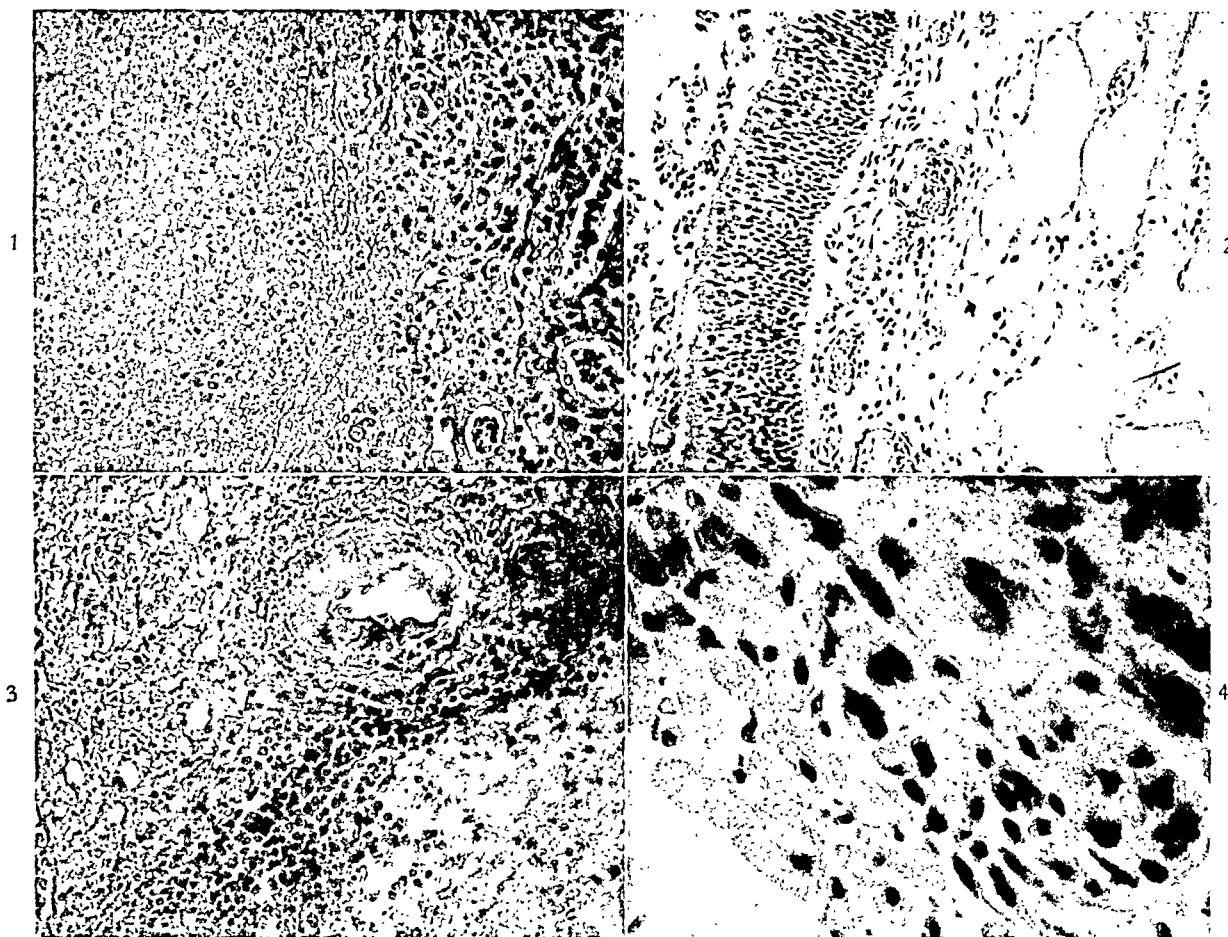


FIG. 1. "Carbuncle" of the kidney. Chronic pyocyanus infection followed by sudden onset of renal pain. Extensive necrosis (left). Evidence of pyelonephritis in renal tubules (right).

FIG. 2. Allergic coryza. Extreme edema and hyperemia. Slight cellular infiltration. Extruded cells at left include many eosinophile leukocytes.

FIG. 3. Periarteritis nodosa. Necrotizing arteriolitis. Notice fibrinoid necrosis of only part of the wall of the vessel.

FIG. 4. Aschoff nodule, acute rheumatic myocarditis.

evidence that the Aschoff nodule in the myocardium in rheumatic fever (Fig. 4) is the result of anaphylactoid hypersensitivity. It is therefore included in this group although it shows some anatomic characteristics of the granulomatous lesions described below. The extramyocardial lesions of rheumatic fever, however, definitely belong with the granulomatous lesions.

GRANULOMATOUS ALLERGIC REACTIONS

A granuloma is a nodular, almost tumor-like structure made up of inflammatory cells which have proliferated locally. Some granulomas, including some of those we shall discuss below, are of macroscopic size which the foregoing definition intimates; but a large number of them, and certainly

the units of which even the larger ones are composed, are microscopic nodules. All granulomas are the result of inflammation but not all of them are the result of infection. Thus, a very important class of granulomas is due to foreign bodies or to hemorrhage or other degenerative phenomena. The essential structure of all the allergic granulomas consists of a central area of necrosis surrounded by proliferated reticuloendothelial cells which often assume a radial, palisaded arrangement. Other features of the granulomas are variable and probably have little or no relation to the allergy. Giant cells, either of the foreign body type or of the Langhans type, may or may not be present. They may be entirely absent in tuberculosis (Fig. 5) and may be

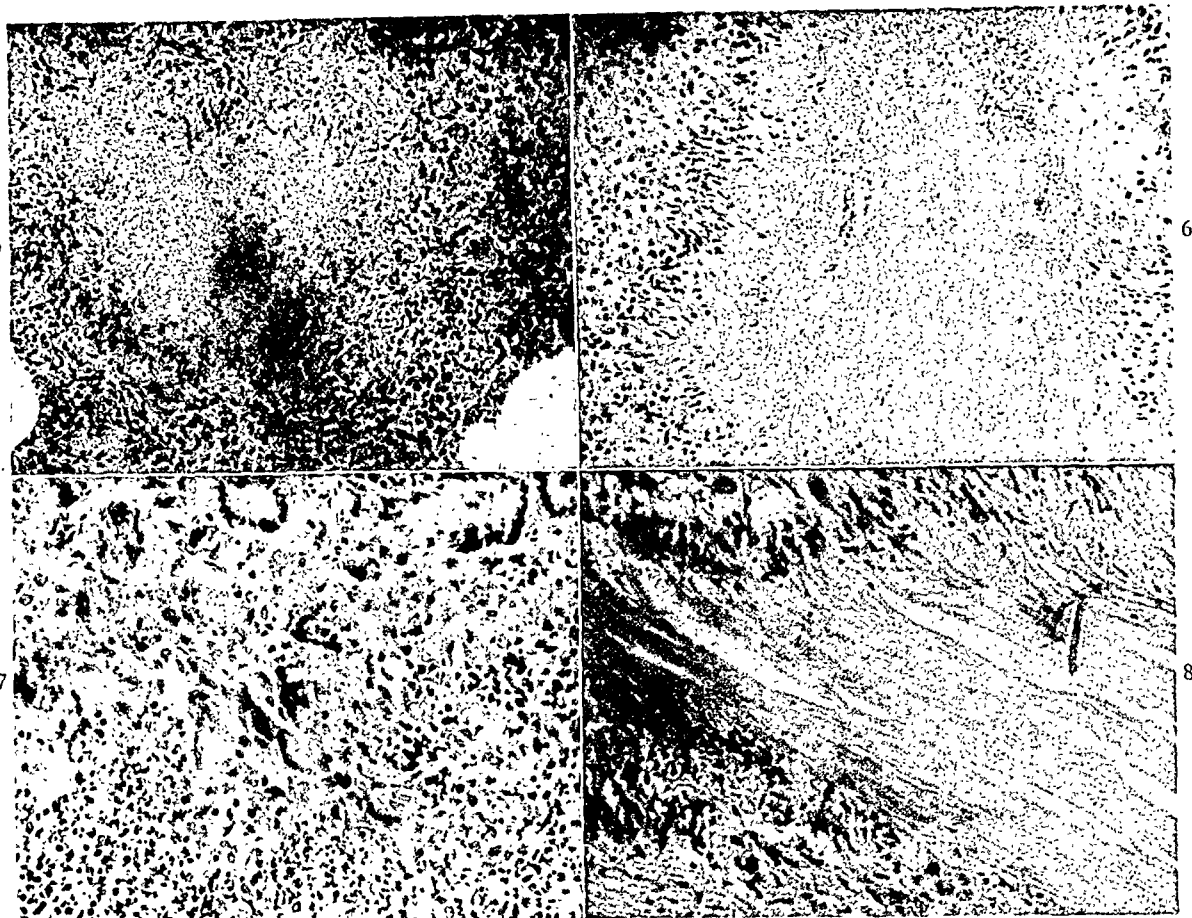


FIG. 5. Tuberculosis. In this case almost none of the tubercles showed giant cells. Tubercle bacilli were numerous.

FIG. 6. Rheumatoid granuloma. Skin nodule in the scalp.

FIG. 7. Granuloma in a case of periarteritis nodosa; many giant cells.

FIG. 8. Rheumatoid scleritis. Fibrinoid necrosis of the collagen surrounded by granuloma.

very numerous in non-tuberculous granulomas. (Fig. 8.) The suspicion of tuberculosis every time a giant cell is present is one of the most reliable evidences that the pathologist is an amateur. Non-allergic granulomas may have all the features of the allergic granulomas except that they lack necrosis.

In some allergic granulomas the central area of necrosis is in the proliferated inflammatory tissue and is called caseation necrosis. In others the necrosis is in pre-existing collagen and is called fibrinoid necrosis. This anatomic difference delimits two groups of granulomatous allergic lesions, the *tuberculoid* and the *rheumatoid*. It is a remarkable fact that these two groups are also differentiated by clinical phenomena: The tuberculoid granulomas are all caused by well known living agents and give posi-

tive tuberculin-like skin tests with appropriate antigens; while in the rheumatoid lesions no single living agent has been identified as the cause, (there is, indeed, reason to believe that there may be more than one cause) and no characteristic skin tests are known.

Tuberculoid Allergic Lesions. At one time the histologic diagnosis of tuberculosis was a matter of utmost simplicity. Gradually it has been recognized that there are many nodular lesions which resemble tuberculosis but are not tuberculous. On the one hand there are foreign body reactions (especially those due to silicates, including talcum granulomas) and sarcoidosis, all of which lack central necrosis. On the other hand there are infections such as brucellosis, tularemia, sporotrichosis, lymphopathia venereum and coccidioidomycosis. Tubercle

bacilli are, therefore, searched for in tissue sections today more often than they were a generation ago.

The characteristic tubercle occurs as a reaction to tubercle bacilli only after sensitization to tubercle bacilli has been established.³⁰ There is good reason to believe that the necrosis is entirely the result of tuberculo-protein acting in a sensitized subject. The peripheral portions of the tubercle, and particularly the giant cells and histiocytes, can be elicited by dead tubercle bacilli or by lipid fractions of tubercle bacilli. Lipoids, it will be remembered, are the most potent single excitant for giant cell production.

One of the non-caseating tuberculoid lesions, *sarcoidosis*, deserves special mention because of its clinical relationships to tuberculosis. The histologic lesions of sarcoid lack the necrosis of allergic granulomas; correspondingly, they almost always have a negative tuberculin skin test and therefore lack clinical evidence of tuberculo-allergy. Tubercle bacilli are rarely found in sarcoid lesions but occasionally are fairly numerous. (Fig. 5.) I have seen lesions histologically identical with sarcoid (even showing asteroid inclusions in giant cells) around foreign bodies (plant cells, talcum, lipid accumulations). For these and other reasons I think it is probable that sarcoidosis is essentially a foreign body reaction in which non-pathogenic tubercle bacilli are commonly the exciting foreign body.*

The caseating tuberculoid lesions may all appear the same on histologic examination. They have this feature in common, that in all of them positive skin tests of the tuberculin type may be obtained. It is probable that the similarity in histologic structure is due to the similar kinds of allergic states and that the minor differences, more of statistical than of pathognomonic importance, are due to differences in the causative micro-organisms.

* I once mentioned this notion to Dr. Paul Klemperer who intimated that he held similar ideas (I hope I am not misrepresenting him) and in support he read to me a reference to the fact that non-pathogenic tubercle bacilli have higher lipid content than pathogenic ones.

One word of caution and just one indication that the pristine simplicity of classification must not be gulped down whole. Histoplasmosis is a fungus infection in which positive tuberculin-like skin tests can be obtained with appropriate antigens (histoplasmin). Yet its histology does not even faintly resemble allergic reactions of any kind but instead consists of a simple stuffing of reticulo-endothelial cells with fungi. Does this reticulo-endothelial "blockade" alter the tissue reactions? Or is it relevant at this point to know that the specificity of the histoplasmin reaction has been questioned?

Rheumatoid Granulomas. The subcutaneous nodules, joint lesions and the less common lesions of both rheumatic fever and rheumatoid arthritis show very similar histologic structure. (Figs. 6 and 8.) The characteristic features of these lesions is the fibrinoid necrosis of *pre-existing collagen* in the centers of the granulomas. The necrosis tends to be more marked in the lesions of rheumatic fever which corresponds to the more rapid clinical course of this lesion as compared with most cases of rheumatoid arthritis. This and other minor differences in the frequency with which some parts of the granuloma occur in rheumatic fever lesions on the one hand and in rheumatoid arthritis on the other are slight and insufficient to distinguish the two on histologic grounds.³¹

There exist certain lesions whose structure is basically that of the rheumatoid granulomas but whose relation to rheumatoid lesions is still disputed. One group of these will serve as an example. Two lesions of the sclera have been described, both of them rare, which have identical histologic lesions resembling the rheumatoid granuloma. Differences in the distribution of the lesions in the sclera and certain minor clinical differences have been described in brawny scleritis^{32,33} and scleromalacia perforans.^{34,35} Based on the very small number of reported cases, it is said that scleromalacia perforans is regularly associated with rheumatoid arthritis, whereas brawny scleritis is usually

not so complicated. Recently we have seen an instance of this kind in which the arthritis was severe, the clinical features of both scleromalacia and brawny scleritis were present and the distribution of the lesions was that of both conditions. The essential elements of the histologic lesions were those of rheumatoid granulomas. (Fig. 8.) We believe that the similarities between these two diseases are more important than the minor differences and we propose that the two be subsumed under the single designation, "rheumatoid scleritis."³⁶

More common than the eye lesions are granulomas in the respiratory tract, especially in the nose. These often contain large numbers of giant cells and have frequently been called "giant-cell granulomas." Their lethal nature has been well known.³⁷ Rössle³⁸ first identified them as accentuated forms of "rheumatism" and noted their relation to vascular lesions. They were then described as occurring in borderline forms of periarteritis nodosa³⁹ and finally several reports appeared^{23,40} in which the granulomas and periarteritis nodosa were definitely associated. Figure 7 is from a recent case in which, after the usual misdiagnosis of tuberculosis (see the giant cells), the diagnosis of granuloma and periarteritis nodosa was made from a nasal biopsy.

In spite of the striking evidence that the lesions in this group are characteristically allergic, the absence of immunologic corroboration makes their position somewhat equivocal and their location in Table 1 is intended to portray this fact.

SUMMARY

An attempt to classify the histologic lesions seen in allergic diseases is herein presented. It is shown that anatomic differences in these lesions divide them into a relatively small number of groups, each of which has not only a certain histologic identity but clinical and immunologic similarities as well.

Pathognomonic significance cannot be claimed for any of the lesions described

but all of them are highly characteristic and their presence suggests allergy as a possible cause. Many of the lesions can, no doubt, be caused by both allergic and non-allergic mechanisms.

The position of some of the diseases in this classification is uncertain and may have to be changed. It is hoped, however, that the classification may suggest considerations which will clarify these anomalous positions and lead to a more useful classification.

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The Immunology of Allergic Disease*

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IN writing on allergy, especially in its broader phases, it is still necessary for the author to interpret what he means by the word. This is more readily done by explanation than by definition. That state of well being which we call health results from the proper or normal action, reaction and/or interaction of the vital cells of the body. Disease, however, for the most part is the response of cells to an abnormal environment that is created by too much or too little of the normal products of nutrition, or of the various glandular secretions or is the result of poisons from without or within including those of invading bacteria and viruses. All of these disease-producing factors exhibit more or less widespread evidence of organic or functional disease through their *direct* effect or action, either positive or negative, on various tissue cells.

On the other hand, there is another group of agents which produce toxic effects by *indirection*. They are those substances, themselves usually harmless, which exert profound and even lethal effects upon tissue cells because of a specific sensitization. Such reactions, when mediated by an antibody mechanism, constitute allergy.

Under this broad interpretation many manifestations are encountered with varied etiology, pathology, immunology and symptomatology, affecting the cells of many tissues and organs and often having no apparent relationship. However, a common denominator which justifies the use of the word "allergy" can, I think, be found in the fact that the tissue responses are based upon the proved or reasonably assumed existence of a cellular antibody that has a specific affinity for an antigen which when present becomes linked to the sensitized

cell. This causes a cellular response that is varied, depending upon the character, function or type of cell, the chemical nature of the antigen, the type of contact and the immunologic mechanism. The fact is, however, that the resultant reaction is always "altered" from that of the same substance in contact with non-sensitized cells.

This concept of allergy is somewhat at variance with the original "altered reactions" for which the word allergy was coined by Von Pirquet;¹ he was describing the quantitative variations of the anamnestic reaction rather than the qualitative changes which result from an existing sensitization and for which the word has been appropriated.

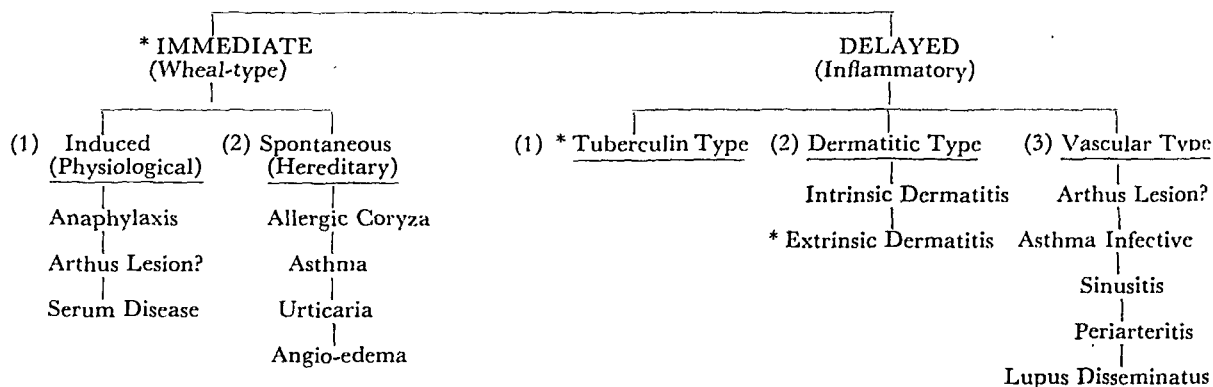
As to the details of the chemistry and pharmacology of those substances which are derived from the action of antigen on sensitized cell, there is still little precise knowledge. In that immunologic reaction exemplified by animal anaphylaxis and by serum shock, studies have shown that histamine or a histamine-like substance is at least one of the toxic agents released from the cells in which it exists in a bound state. Through its pharmacologic action on cells histamine produces edema and hyperemia which are characteristic of the immediate wheal-type allergic reactions. Under appropriate conditions smooth muscle contraction also occurs. But this is about as far as one can go today. Why *tuberculin* produces its inflammatory effects only on those cells sensitized by a prior tuberculous infection and why the phenols of plants like poison ivy produce the irritative reaction of dermatitis only on persons previously sensitized to the plants is not known. On *aprici* grounds there must be other agents

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than histamine for the action upon sensitized cells of tuberculin, poison ivy and similar allergens bears no resemblance to those effects which histamine or other products of the anaphylactic reaction are able or known to produce. This thought is

diseases of man and the subsequent studies in the field of human allergy, it has become clear that certain types of sensitization are readily developed artificially in animal and man to such an extent that they must be regarded as normal or, as I³ originally

ALLERGY (Antigen-sensitized Cell Reactions)



* Antibody mechanism has been demonstrated.

entirely in keeping with and analogous to that of Menkin² who has described the many agents in inflammatory exudates such as leucotaxin, necrosin, pyrexin and the leukocytosis promoting factor, each producing its own special effect.

AN IMMUNOLOGIC CLASSIFICATION

When one observes the different types of accepted antigen-antibody activity, one single fact stands out above others: Either the reactions are "immediate" (within one hour) or they are "delayed" for several days, assuming of course the pre-existence of the sensitized state; for example, the development of serum disease after the normal incubation period does not represent delayed reaction, for once antibody has been produced, the reactions of antigen on sensitized cell are prompt.

On this basis an attempt has been made to schematize the various reactions, and while such a classification as the following may not and probably will not be entirely adequate or permanent, it will serve as a framework for this immunologic discussion.

IMMEDIATE REACTIONS (WHEEL-TYPE)

As a result of the discovery of anaphylaxis, the application of its principles to certain

termed them, *physiologic* responses to antigenic stimulation. This is in marked contrast with a group of human (occasionally animal) reactions that develop spontaneously and in which an hereditary factor plays a significant rôle. As we see it today, practically all human beings are sensitized by heterologous serum (90 per cent⁴), by the phenols of ivy (70 per cent⁵), by tuberculous infection (100 per cent) and by certain drugs (nirvanol 80 to 90 per cent); whereas only a small fraction of mankind⁶ (10 per cent) develop the spontaneous clinical allergies upon natural exposure to airborne and ingested allergens.

However, the hereditary factors involved in both artificial and spontaneous sensitization are extremely complex. In animals the importance of heredity was demonstrated by Webster⁷ in strains of mice with high and low susceptibility to mouse typhoid infection and by Chase⁸ who developed strains of guinea pigs with high and low susceptibility to sensitization (dermatitis) with simple chemicals and poison ivy. The fact is that clinical studies^{6,9,10,11} in man have shown that heredity is certainly a significant factor in the spontaneous allergies of man and may likewise be a factor, though less apparent, in susceptibility to

sensitization on contact with known allergens. A recent paper by Neel¹² discusses more fully the complexity of the genetic factors involved in inherited disease. There are very considerable differences in the degree of susceptibility of man to parenteral injections of horse serum; but 10 per cent develop serum disease after small (5 to 10 ml) doses whereas with large amounts (100 ml) the symptoms occur in '90 per cent. That this susceptibility is individual and selective as well as dependent upon factors of antigenicity is indicated by the studies of Landsteiner et al.¹³ and by general clinical observation.

INDUCED ALLERGIES

Animal Anaphylaxis. Since Richet's¹⁴ work on actinia in 1902 and that of Theobald Smith¹⁵ on diphtheria antitoxin in 1904, anaphylaxis has been extensively studied and is the basis for the concept of human allergy. When a small dose (0.1 to 1.0 ml) of horse serum is parenterally injected into a normal guinea pig, there is no observable effect. When this dose is repeated in a week or ten days or after longer intervals (up to two years), there is an immediate reaction (anaphylactic shock) with dyspnea, cough, convulsions and frequently death in a few minutes though the animal may recover.

Members of almost all of the animal kingdom appear to be susceptible to sensitization in varying degrees but the guinea pig appears to be most readily sensitized and the rhesus monkey one of the least. Regardless of the antigen used, the symptoms are the same in any one species but vary widely in different species. In the guinea pig death is due to asphyxia from bronchospasm but there is also contraction of all smooth muscle. The lungs are markedly emphysematous. In the dog there is vomiting, bloody diarrhea and collapse. The liver and abdominal organs are engorged with blood due to contraction of the muscle pads of the hepatic veins. The rabbit suffers circulatory failure with dilatation of the right side of the heart caused by spasm of the pulmonary vessels. The anaphylactic

reaction in the horse is evidenced by edema and urticaria. In all animals the reaction is prompt with smooth muscle spasm and increased capillary permeability; in other words, the reaction is basically the same though symptoms vary with the species.

It was on the basis of the similarity of species reactions, regardless of the antigen, that Dale¹⁶ suggested histamine as the long sought anaphylatoxin. There are some very sound reasons for believing that this is so, in part at least, but this has been reviewed by Feldberg¹⁷ and by St. Went¹⁸ and is discussed in Rose's article in this symposium. It need not be elaborated here except to state my belief that histamine can be the factor only in the *immediate* wheal-type allergies.

The antigens responsible for this induced anaphylactic sensitization are usually proteins, in some cases proteoses; but simple chemical compounds of low molecular weight in general do not act as antigens unless combined as a haptene with a protein, in which case the simple chemical may be the determinant or specifically reacting group rather than the protein. The exceptions are phthalic anhydride, producing sensitivity in man (Kern),¹⁹ and citraconic anhydride used by Jacobs et al.²⁰ and Landsteiner and Chase²¹ in guinea pigs.

To produce sensitization the antigens may be administered by any parenteral route; in the guinea pig sensitization has been accomplished as well by ingestion and inhalation of protein distinctly foreign to the animal. Shock is elicited by parenteral injection of antigen after an incubation period of eight to twelve days. The reactions are most striking after an intravenous dose.

That sensitivity has developed may be demonstrated in any one of several ways: (1) by anaphylactic shock; (2) by passive transfer of sensitivity, that is, if a sensitized animal is bled and its serum injected into a non-sensitive animal even of another species (e.g., rabbit to guinea pig), the latter after a short period (four hours) will show shock when injected with the original antigen;

and guinea pigs born of a sensitized mother also may be shocked by an injection of the specific antigen, thus showing placental filtration of the sensitizing antibody; (3) by *in vitro* tests, precipitation and complement fixation in the presence of antigen; (4) by the Schultz-Dale reaction, the *in vitro* contraction of smooth muscle of the uterine or intestinal strip on addition of antigen; (5) by the injection of sensitive serum (human, guinea pig or rabbit) into the skin of normal man.^{22,23,24,25} Such a site tested after a few hours with the antigen may show a typical urticarial wheal.

There are then, excepting the active shock reaction, three useful tests by which antibody may be demonstrated in the serum of the sensitized animal; the precipitin test, the Schultz-Dale test for smooth muscle sensitizing antibody and the passive transfer to human skin of the skin sensitizing antibody. The evidence that these tests are dependent upon separate and distinct antibodies lies in the fact that quantitative correlation between them is not always demonstrable. One may find a high precipitin titre and low sensitivity capacity by passive transfer and vice versa. The relation of these antibodies to those found in man after serum disease and in such spontaneous allergies as asthma will be discussed later.

Another phase of animal anaphylaxis should be mentioned. *Desensitization*²⁶ by the injection of sublethal amounts of antigen is readily accomplished. During this time large doses of antigen may be given without the production of symptoms and an animal may be kept desensitized by frequent repeated injections of antigen. In fact, such doses may produce a state of clinical immunity even though anaphylactic antibodies are demonstrable in the serum. In short, the line between sensitization and immunity is not well defined nor is the mechanism of this immune state thoroughly understood at this time.

The *Arthus phenomenon*²⁷ should be mentioned in this connection. While it may occur in other species, it is produced notably in rabbits. Repeated subcutaneous injections

of protein ultimately produce a local inflammatory response which may proceed to necrosis. This is due to the fact that the reaction takes place chiefly in the walls of blood vessels. It is not, therefore, an essential part of the anaphylactic reaction *per se* and confusion arises from the fact that the anaphylactic antibodies are also present as a result of the sensitizing procedures. Histologically, these reactions are more closely related to those lesions which Rich²⁸ has described in rabbits and man following administration of serum and sulfonamides and are closely related to, if not identical with, those of periarteritis and disseminated lupus. The immunologic mechanism of the Arthus phenomenon and of the related vascular lesions is not fully understood.

Serum Disease and Post-serum Disease Sensitization. Serum sickness is the term applied to the reaction which develops in normal man seven to twelve days after a primary injection of serum. Its incidence varies from 10 to 90 per cent and, as previously stated, is roughly proportional to the size of the dose. The main symptoms are urticarial eruption, fever, arthralgia and lymphadenitis. Occasionally, the central and peripheral nervous system is involved, presumably an edema of meninges or nerve sheath. Fatalities are practically unknown. There may be several recurrences in rapid succession, probably reactions to the different serum proteins.

Among the many immunologic studies, those of Longcope and Rackemann²⁹ and Mackenzie^{30,31} especially have thrown light upon the mechanism underlying this disease. During the incubation period the heterologous serum may be demonstrated in the blood. With the onset of symptoms, antibodies (precipitins) appear and with their increase the foreign antigen rapidly disappears from the blood. The symptoms are caused by a reaction of the newly formed cellularly attached antibodies and the residual antigen. The symptoms disappear with the removal of antigen from the body which is then left in a state of sensitization entirely analogous to that of the anaphylac-

tic animal. This state of cellular sensitization is readily shown in man by a positive immediate wheal reaction on skin and eye test with the appropriate serum. The antibodies are also demonstrable in the serum for they will precipitate antigen *in vitro*, passively sensitize guinea pigs (Schultz-Dale) and transfer sensitivity to the skin of normal man. In man this state of reactivity is usually temporary (for weeks or months) though Mackenzie³¹ has reported sensitization to serum lasting from two to eight years. Von Pirquet and Schick³² showed that in those who had had previous injections of horse serum and lost their sensitivity, the incubation period was shortened considerably after a later injection; that is, the reaction was accelerated, a form of the anamnestic response of cells trained by previous stimulation.

In man, anaphylactic shock has occurred as in the animal when a second injection of antigen is given after a seven to twelve-day incubation period, or even weeks later, although the initial injection caused no symptoms. These cases are of course accidental and understood only in retrospect, hence have not been carefully studied. The reactions have been caused, as a rule, by secondary injections of heterologous antisera, liver extracts, tetanus toxoid (proteose) and viral vaccines produced in egg yolk. Reference will not be made here to the shock reactions following *primary* injections for these are an evidence of spontaneous allergy and should not be included in this group.

SPONTANEOUS (HEREDITARY) ALLERGIES OF MAN

Such diseases as asthma, hay fever (both seasonal and perennial), dermatitis (infantile eczema), urticaria and angio-edema are accepted allergies in which hereditary factors have been shown to be significant. Certain patients with disturbances in the central and peripheral nervous and gastrointestinal systems, when due to foods or drugs, may also belong in this group.

The common allergens include airborne

pollens, danders, mold spores, various dusts encountered at home and at work as well as foods and drugs. The reason why one individual becomes allergic to one substance and another to a different one is not known. The offspring of allergic parents inherit not a specific sensitization but the capacity or tendency to be allergic.⁶ There is no placental transmission of sensitizing antibody in these spontaneous allergies of man.^{33,34} Presumably, contact is a determining etiologic factor in many cases as indicated by a sensitivity to castor bean in those living near a bean-processing plant and an increasing allergy to the pollen of sugar beet which Phillips³⁵ showed followed the introduction of sugar beet in a restricted area. But many persons develop a high degree of sensitivity when there has been no apparent contact, as evidenced by the severe shock reactions following the first injection of horse serum which occurred not infrequently in the earlier days of treatment with diphtheria antitoxin.³⁶

The pathologic reaction is one of vasodilatation and increased capillary permeability with edema which takes place in all sensitized tissues, especially skin and mucous membrane. In the latter, the reaction also stimulates mucoid secretion which is a conspicuous feature of hay fever, asthma and of reactions of this type in the intestinal tract. Such allergies are usually accompanied by an excess of eosinophilic leukocytes in the tissues, in their secretions and in the circulating blood.

Clinical Studies. The outstanding characteristic of these reactions is their promptness, both symptomatically and by test. The person who has asthma and is sensitive to cats develops the asthmatic reaction promptly, perhaps in five minutes, certainly within an hour, if adequately exposed. This may mean simply entering a home where cats are house pets. If one skin tests this person with an extract of cat dander, there is an immediate wheal-type reaction at the test site; and if one injects the serum of a cat-sensitive person into the skin of a normal person and then tests the site with

the cat dander extract, the same prompt wheal is produced. This is known as the Prausnitz-Küstner²² phenomenon of passive transfer of sensitiveness. The point is that no matter how the skin test is done, directly or indirectly, the reactions are always immediate with wheal formation only; that is, they are temporary and completely reversible. The clinical reaction in the mucous membrane is the same immediate edema as is the skin test and the symptoms referable to the respiratory tract, both vasomotor rhinitis and asthma, are due to the reaction of the lining membrane of nose, bronchi and bronchioles. The significant point is that if a test reaction is an immediate edema the clinical reaction will also be an immediate edema in the sensitized tissue. Immunologically, histologically and clinically, the test response and the clinical reaction must be of the same kind. This is basic and pertains to all types of allergic reactions.

An allergic reaction takes place only in the sensitized cells. It is to be expected then that persons with this type of allergy, that is, of the mucous membrane of the respiratory tract, would have as causes for symptoms mainly those inhaled airborne substances such as pollens, animal emanations and dusts of various sorts and, much less frequently, ingested foods or drugs.

In addition to asthma and hay fever, the reactions of the immediate wheal-type also express themselves clinically as urticaria and angioedema reactions of skin and gastrointestinal tract, usually caused by ingested foods or drugs and very rarely by inhaled allergens.

If a person after eating fish or shell fish develops urticaria within one hour, often with associated gastrointestinal symptoms, the type of allergy concerned is identical with that found in pollen hay fever, for one quite regularly obtains a positive skin test and passive transfer of sensitivity by serum to a normal skin. Patients with such immediate reactions to certain foods usually relate cause and effect and abstain from their use. They rarely need a physician to

confirm a diagnosis they have made for themselves. It is in this form of allergy and in this alone that the wheal-type of skin test is useful in determining or confirming a specific cause.

However, there are edema reactions that appear to be exceptions to this rule. Many patients with urticaria and angio-edema do seek medical aid because they cannot relate cause and effect for themselves since the clinical response is not immediate but may be delayed for four to twenty-four hours or more. These reactions, originally described by Cooke,³⁷ are important because they are common, especially in patients with symptoms referable to viscera and to the central nervous system and because the usual diagnostic approach with skin tests is of no avail. The explanation for certain of these cases is afforded by studies reported by me³⁸ a few years ago and confirmed by Blamoutier.³⁹ One of the patients then described illustrates the point. He had abdominal pain and diarrhea four to five hours after ingestion of milk. Once the allergen was determined, the attack was regularly reproduced and always after the specified incubation period of four to five hours. The skin test with whole milk was negative but it was positive with a proteose fraction of milk. The delayed appearance of the reaction is explained by the fact that it takes about four hours for the patient to digest milk to the stage in which it becomes allergenic. Immunologically, it is the same immediate wheal reaction but clinically it has the appearance of a delayed reaction. These cases are difficult diagnostic problems. The fixed incubation period is the clinical criterion for it remains the same in the particular patient for the particular food.

Serologic Studies. The Skin-sensitizing Antibody: When one studies the serum of untreated patients with spontaneous allergy of the immediate wheal-type, such as hay fever, using the various laboratory technics as applied in the work on anaphylaxis and serum disease, interesting characteristics appear.⁴⁰ No precipitate has yet been shown by the addition of antigen to the serum *in*

vitro and there is no demonstrable combination of antigen with the antibody *in vitro*. Presumably it can combine only after the antibody has become cellularly attached when a wheal reaction will ensue. When the serum is injected into guinea pigs, they are not sensitized passively, that is, they cannot later be shocked, neither is the Schultz-Dale reaction positive; in other words, there is no evidence of an antibody that will sensitize smooth muscle and produce bronchospasm or uterine contraction. Such serum injected into rhesus monkeys will sensitize the skin and mucous membrane and give immediate wheal reactions to antigen, as shown by Straus,⁴¹ but there has been no evidence of any smooth muscle response. When this sensitive serum is injected intradermally into a normal man, the site will respond specifically when tested with the antigen a few hours later. The response is an immediate wheal and the site is readily desensitized. When sensitive serum is injected intravenously a general sensitivity may result with a clinical response (asthma), as reported by Ramirez⁴² who cites a patient with pernicious anemia transfused with blood of an asthmatic allergic to horse dander. This work has been confirmed by Loveless.⁴³ Such passive sensitivity is temporary, for days or weeks only.

The skin-sensitizing antibody exists in the serum of the spontaneously allergic person in large amounts for serum diluted several thousand times may still give positive reactions on transfer to the skin of normal test-subjects.⁴⁰ This antibody does not pass the human placenta^{33,34} for it is not found in cord blood. An interesting characteristic of this antibody is that it does not carry a high degree of specificity, nothing comparable to that of artificially produced precipitins, as shown by direct tests or by cross-neutralization experiments.⁴⁰ It is destroyed by heating the serum at 56°C. for four hours⁴⁴ and in this way differs from the artificially produced blocking antibody to be described.

In summary, then, the skin-sensitizing antibody in the spontaneously sensitive man

has never yet been proved to act as a precipitin and cannot sensitize smooth muscle but has an affinity for cells of skin and mucous membrane. There is no evidence that it can combine with antigen except in these cells. It is spoken of as a skin-sensitizing antibody and has been referred to at times as reagin.

Cooke and Spain,²³ using precipitin (Schultz-Dale) and passive transfer tests, made comparative serologic studies, later confirmed, of rabbits sensitized to horse serum (anaphylaxis), of man after serum disease from antitoxin and of an asthmatic spontaneously sensitive to horse serum. The significant differences that appeared may be tabulated as follows, the average extent of reactions being indicated by the number of plus (+) signs:

	Pre- cipitin	Smooth Muscle (Schultz- Dale)	Passive Transfer to Human Skin
Artificially sensitized animal..... (anaphylaxis)	+++	+++	+
Artificially sensitized man (serum disease)	+++	+++	+++
Spontaneously sensitized man..... (asthma)	0	0	++++

These studies, abundantly confirmed, show that the antibody that sensitizes the skin of the naturally sensitive man (asthma) is not a precipitin nor does it sensitize smooth muscle. Whether this is the same antibody that sensitizes skin and gives positive reactions after artificial sensitization in man (serum disease) or animal (anaphylaxis) has not been determined nor does any experimental approach presently appear available.

The moot question is whether the artificially produced antibodies in man and animal are one and the same, that is, is the precipitin the anaphylactic antibody? The majority of immunochemists working in

this field believe that it is and that the amount of precipitin is a measure of the sensitizing capacity of a serum. This is discussed by Kabat. It should be pointed out that present technics of active sensitization would be expected to stimulate all possible types of antibody concurrently and these would probably lie in the same protein fraction of serum and so might be separated with difficulty if at all. One tends to rely then on a quantitative correlation which does not always appear. The question of identity of precipitin, muscle-sensitizing and skin-sensitizing antibody cannot be fully resolved at this time.

The clinical value of the treatment of such allergies of the immediate wheal-type as hay fever has been established. By injections of the specifically reacting pollen extract, given over periods of several months, tolerance for the antigen is increased several hundred-fold and protection against clinical exposure is likewise increased.

Desensitization such as is produced readily in the anaphylactic animal does not obtain in the naturally sensitive man. In the early stages of treatment the amount of skin-sensitizing antibody in the serum is actually increased⁴⁵ and decreases only after prolonged treatment. A decrease of sensitivity of the tissues of the skin and conjunctiva is only partial at best and that only after weeks of treatment. The effect of therapeutic injections of specific allergens then may be spoken of rather as one of hyposensitization, possibly immunity, but not desensitization.

Blocking Antibody. Serologic studies⁴⁶ of patients treated for hay fever by means of specific pollen injections have shown the presence of a second antibody demonstrable by the fact that it has the capacity to inhibit the action of antigen on cellularly attached sensitizing antibody in skin sites when the serum of a treated patient is first mixed *in vitro* with the antigen and then used as the testing antigen. This is well shown in Table 1. Sites were made on the back of a normal test subject (D. L.) five each for ante- and post-treatment serum dilutions (1-10 to 1-500) for later testing

with antigen. Sites were also made with the ante- or post-treatment serum to which antigen (ragweed extract) was added in the strength indicated (neutralization tests). The immediate reactions at these latter sites were read after one hour and it is

TABLE I
COMPARISON OF ANTE- AND POST-TREATMENT SERUM
(BUSCH)*
Normal Test Subject D.L. Used for Passive Transfer Test

Dilution Tests		Neutralization Tests			
Serum Dilutions†	Reaction to test‡	Mixtures Made with Equal Amounts of§		Reaction of Sites	
Ante-treatment			Ragweed Units per ml.	1 Hr. after Sites Were Made	On Retest
1-10	+++	Busch Serum			
1-100	++	Ante-treatment	50	+++	0
1-200	++	Ante-treatment	100	+++	0
1-300	+	Ante-treatment	150	+++	0
1-500	±	Ante-treatment	Saline	0	++++
Post-treatment	Post-treatment	150	0	++
1-10	++	Post-treatment	300	0	++
1-100	++	Post-treatment	500	0	+
1-200	+	Post-treatment	700	0	++
1-300	0	Post-treatment	1000	±	+
1-500	0	Post-treatment	Saline	0	+++

* COOKE, R. A. *J. Allergy*, 15: 212, 1944.

† $\frac{1}{10}$ ml. of the stipulated dilutions of serum in physiologic saline was injected into each site.

‡ The serum dilution sites were tested forty-eight hours later with $\frac{1}{40}$ ml. low ragweed extract, 100 protein nitrogen units per ml.

§ $\frac{1}{10}$ ml. of these serum-ragweed or serum-saline mixtures was injected into each site.

|| The serum-ragweed or serum-saline mixture sites were tested forty-eight hours later with $\frac{1}{40}$ ml. low ragweed extract, 100 protein nitrogen units per ml.

noted that there were reactions with ante-treatment serum antigen mixtures but none with mixtures made with post-treatment serum. When these same sites were retested two days later, even 50 units per ml. of ragweed extract neutralized the antibody in ante-treatment serum (since retests were all negative), but 1,000 units per ml. of ragweed failed to neutralize the post-treatment serum. This cannot be due to absence of antibody which was shown to be but slightly reduced by dilution test.

Such results are best interpreted as due to the development of an inhibiting or blocking antibody following treatment of

the patient with injections of pollen extract. There are several features that stamp this blocking antibody as distinct from the skin sensitizing antibody: (1) It may be produced easily in non-allergic persons by parenteral injection⁴⁷ whereas the skin-sensitizing antibodies have not been produced in this way. (2) It has further been shown that the blocking antibody, unlike the skin-sensitizing antibody, has no tissue affinity for it readily passes placental membranes³⁴ and is found in cord serum of infants from treated mothers. (3) It differs in that it binds antigen although it does not form a precipitate. (4) It has an almost absolute specificity which the skin-sensitizing antibody does not possess.⁴⁰ (5) The blocking antibody is thermostable and unharmed at 56°C. for four hours⁴⁴ whereas the skin-sensitizing antibody is destroyed at this temperature.

Blocking Antibody and Immunity. It is still a moot question whether this blocking antibody produced by therapeutic injections is the important protective antibody or not. Except for the work of Loveless,^{48,49} the studies^{50,51} thus far have not indicated the degree of correlation between the amount of blocking antibody and the degree of clinical immunity that would seem to be required. My own unpublished observations are in accord with the latter studies. Admittedly these clinicoserologic studies are technically difficult and time-consuming and subject to the errors inherent in any appraisal based solely on the patient's impressions of his relative freedom from symptoms. Further, one must take into account the fact that there are at least several different and clinically active antigens in pollen extract with a blocking antibody specific for each.⁴⁰ None of the work thus far has taken this last fact into account. Also, patients who react to pollen extracts yet are clinically free, that is, immune in the real sense, frequently do not show blocking antibody in their serum.⁴⁰ They must therefore have some other as yet undiscovered protective mechanism. The fact that the blocking antibody has no cellular affinity makes it diffi-

cult to understand how it could protect the respiratory mucous membranes against airborne pollen whereas it could protect against injected (therapeutic) pollen extract, and this it may well do, thus permitting the increasing dosage during treatment. The studies of Sherman⁴⁵ strongly suggest this.

DELAYED ALLERGIC REACTIONS

There are three types of delayed reaction that may be differentiated for the present at least on certain obvious clinical and histologic grounds:

Tuberculin Type Allergy. Before the days of anaphylaxis and allergy, Koch⁵² showed that tuberculous animals were reactive to the products of the growth of tubercle bacilli (tuberculin) which could produce either death or a local cutaneous reaction in the infected animal. This tuberculin skin reaction was a delayed twenty-four to forty-eight hour inflammatory response that was specific. Though bacterial protein may give rise to anaphylactic sensitization,^{53,54,55} this delayed response was shown by Zinsser⁵⁶ to be entirely different. Animals cannot be made sensitive to tuberculin by injecting it in any amount, therefore tuberculin does not generate antibody production but merely reacts with preformed antibody. Though sensitivity to tuberculin could readily be created by injecting live tubercle bacilli, it was not until 1924 that Zinsser and Petroff⁵⁷ obtained positive results by intraperitoneal injections of massive doses of dead organisms. Eight to ten days are required for the incubation period for active sensitization. Having mastered the technic for the active production of tuberculin type allergy in non-tuberculous animals, which was facilitated by the use of such adjuvants as paraffin (Couland)⁵⁸ and paraffin oil (Saenz,⁵⁹ Freund⁶⁰), the next question was whether this sensitivity could be passively transferred from sensitive to non-sensitive animals. Beginning with Baldwin's⁶¹ work in 1910, all attempts were in vain until finally (1945) Chase⁶² succeeded in the passive transfer of tuberculin sensitivity.

In his experiments normal guinea pigs were rendered sensitive to tuberculin by massive intraperitoneal doses of dead tubercle bacilli combined with the adjuvants above mentioned. Cells from spleen, lymph nodes and peritoneal exudate of the sensitive animals were washed thoroughly and injected into normal guinea pigs. In practically all experiments these animals became reactive to tuberculin in one to three days instead of the eight to ten days required for active sensitization, depending on the route of injection of the cells. The blood serum of the same actively sensitized guinea pigs did not transfer a sensitivity. Thus Chase has demonstrated conclusively that the mechanism for the tuberculin reaction involves a specific antibody that is strictly cellular, in other words, the reaction is an allergy (antigen-sensitized cell reaction). Rich⁶³ has shown that this cellular reaction is demonstrable in such avascular tissues as the cornea, hence is fundamentally different from the Arthus lesion which depends upon vascularity for its effects.

So far as is known, all bacteria are capable of producing the same specific sensitivity, hence the use of the modifying term "tuberculin-type." A similar skin test may be employed, therefore, as a diagnostic procedure in such other diseases as typhoid fever, brucellosis, tularemia, glanders, syphilis, certain fungus infections and in the viral infections causing lymphogranuloma venereum.

The diagnostic value of all such tests is lessened by the fact that sensitization persists after mild and cured infections, hence the test does not distinguish past from present and active infection.

Dermatitic-type Allergy. For many years certain forms of dermatitis such as infantile eczema have been hypothesized as allergies that is, antigen-sensitized cell reactions on the basis of clinical association with known allergies (asthma and food sensitivities) and because of the dermatitis produced in a few individuals upon slight external contact with chemicals, dyes, metals and plant phenols which are not irritating to the skin

of most human beings. Such lesions when they occur are always delayed twenty-four to forty-eight hour reactions which may go on to vesiculation and exudation.

We are concerned here merely with the discussion of the immunologic aspects about which little is actually known as yet. The questions are, can antibody be demonstrated and if so, is it cellular or is it humoral, or may it be both? Landsteiner and Chase⁶⁴ produced dermatitis in guinea pigs which were sensitized by the application to the skin of picryl chloride. They used the peritoneal exudate to sensitize normal animals. When the picryl chloride in oil was put on the skin of these recipients, "erythematous reactions mostly of high color were apparent the next day." Heating, to kill the exudate cells, destroyed the effect. As they state, "consequently one would be inclined to assume that the sensitivity is produced by an activity in the recipient of the surviving cells, if not by antibodies carried by these."

A great deal of experimental work has been done, largely with external contact type dermatitis, in attempts to demonstrate the mechanism underlying these reactions. The experiments of Naegeli et al.⁶⁵ and Fellner⁶⁶ with excised portions of sensitive skin have given negative or equivocal results. However, Haxthausen⁶⁷ used transplants in two pairs of identical twins, one of each pair being sensitized with dinitrochlorobenzene. Skin flaps were transplanted from A (sensitized) to B (normal) and B to A, likewise from X (sensitized) to Y (normal) and Y to Z. When tested after three weeks, A and X gave strong reactions on the surrounding skin and on the graft whereas B and Y did not react either on the surrounding skin or on the previously sensitized skin flap. Such results certainly indicate a humoral antibody and may well explain the results reported from the use of blister fluid by Urbach,⁶⁸ Ballesterro and Mom⁶⁹ and Spain.⁷⁰

Recent work in my laboratory by Crepea, still unpublished, has shown the transference of dermatitic sensitivity from guinea

pigs sensitized by certain chemicals (plant phenols) to normal guinea pigs by means of the intraperitoneal injection of lymphoid and reticulo-endothelial cells of spleen and lymph glands and also by serum. The dermatitic lesion appears in normal animals within twenty-four hours after the injection of serums or washed cells whereas the incubation period for active sensitization is roughly two weeks and is elicited only by dermal application of the antigen.

Vascular-type Allergies. Rich^{28,71} has reported lesions simulating Aschoff bodies and those of periarteritis in man after administration of heterologous serum and sulfadiazine in man and in rabbits after massive parenteral doses of foreign serum. Pathologically, there is also a resemblance to the Arthus lesions of rabbits. The immunologic mechanism of these reactions is confused just as it was in the past in the case of the tuberculin and the anaphylactic types of reaction with tuberculo-protein. The technic of creating vascular lesions at present produces the anaphylactic antibodies concomitantly. The fact is that the vascular degenerations are delayed reactions as opposed to the immediate anaphylactic reactions. Whether there is a different antibody mechanism for the two remains to be determined.

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Quantitative Immunochemical Aspects of Some Allergic Reactions*

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WHILE the concept of allergic reactions as caused by the combination of antigen with antibody in the tissues is unequivocally established (for earlier studies,¹⁻⁵) knowledge of the severity of the allergic response as a function of the amounts of antigen and antibody involved is quite limited. Indeed there have been sharp differences of opinion among various investigators as to the dependence of the Arthus phenomenon on circulating antibody,⁶ the relative significance of humoral and fixed tissue antibody in the various allergic manifestations,⁷ whether or not circulating antibody protects guinea pigs against anaphylactic shock,⁸ the nature of the refractory state following non-fatal anaphylactic shock⁸ and the role of precipitins in serum sickness.⁹

Careful scrutiny of the mass of experimental data reported suggests a number of reasons for these discordant opinions. Among these are: (1) The use of complex mixtures of antigens, such as horse serum, with the resultant simultaneous production in varying quantities of antibody to an unspecified number of antigens; (2) the tremendous variation in antibody response of individual animals of the same species to a given quantity of antigen, so that very large numbers of animals must be used for statistically valid differences to be detected; (3) species differences in allergic manifestations, in the amounts of circulating antibody formed, and in the capacity of sera of various species to transfer certain sensitivities passively to some species but not to others;¹ (4) limitations of immunologic

methods of assaying sera for antibody and (5) non-specific factors such as the inhibition of anaphylaxis by the injection of foreign protein. This effect led Weil¹⁰ erroneously to the conclusion that an excess of antibody in the circulation protects a guinea pig from anaphylactic shock. Weil injected rabbit serum containing antibodies into guinea pigs sensitized to the corresponding antigen and found that they were protected against anaphylactic shock. As pointed out by Bronfenbrenner,⁸ equally good protection would have resulted had an equivalent amount of normal rabbit serum or of normal serum from another species been used.

The need to take these variables into account has not escaped the attention of certain investigators. Cannon and Marshall,⁶ in their study of the Arthus phenomenon, point out that a correlation between the severity of the Arthus phenomenon and the circulating precipitin was found with purified single antigens, i.e., crystalline egg albumin, while discordant results were obtained with mixtures of antigens (whole serum). The unsuitability of the antigen dilution method of estimating the precipitin content of sera for such studies has also been noted,⁶ as has the superiority of passive anaphylaxis over active anaphylaxis as a means of eliminating the variations in the quantities of antibody produced by individual animals in response to injection of antigen.⁸

Since methods for the quantitative estimation of antibodies in terms of the amount of antibody nitrogen per ml. serum are now

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readily available,¹¹⁻¹³ measurements of the amount of antibody in the circulating blood of an animal immediately prior to or after eliciting an allergic response are easily carried out. In studies on passive sensitization, sera may be assayed for their antibody

TABLE I

RELATION BETWEEN CIRCULATING ANTI-EGG ALBUMIN AND THE SEVERITY OF ANAPHYLACTIC SHOCK INDUCED IN THE ACTIVELY SENSITIZED RABBIT WITH CRYSTALLINE EGG ALBUMIN*

Degree of Anaphylaxis	No. of Animals	Antibody Nitrogen Content of Individual Rabbit Sera before Shock
		mg./ml.
Death	8	0.57 ³ , 0.9, 1.0, 1.2, 2.1, 2.3
+++	5	0.11, 0.46 ² , 1.0, 2.1
++	6	0.06, 0.28, 0.34, 0.57, 1.1
+	11	0.03 ² , 0.06 ² , 0.11, 0.16, 0.28, 0.57, 0.80, 1.0, 1.1
0	20	0.02 ² , 0.03 ² , 0.04 ² , 0.11 ² , 0.28 ⁴ , 0.34 ³ , 0.46, 0.57 ² , 0.90, 1.5

+++ = Severe prostration and shock.

++ = Respiratory difficulties, slight prostration.

+ = slight respiratory difficulties.

0 = No reaction.

Superscripts denote number of rabbits having the same antibody N level. Shocking doses of egg albumin N varied from 2.5 to 40.5 mg. and did not appear to be critical.

* Data from Jackson.¹⁴ Values converted to antibody nitrogen, i.e., 16 per cent of antibody protein and expressed to two significant figures.

content and dilutions containing known amounts of antibody may be injected. Similarly, the allergic response may be elicited by injection of a known quantity of antigen. These procedures, if generally adopted, would provide a degree of standardization and reproducibility in results from different laboratories which would do much to avoid conflict and confusion.

The earliest attempt to estimate the quantities of antibody in the circulating blood of sensitized animals was made by Jackson¹⁴ who studied the severity of anaphylactic shock in rabbits actively sensitized to crystalline egg albumin in relation to the amounts of antibody in their sera. From her data (Table I) it is evident that in the actively sensitized rabbit there is only the most general correlation between

the amount of circulating antibody and the severity of anaphylactic shock in the rabbit and that a high level of circulating antibody does not necessarily ensure fatal anaphylaxis. Indeed, of the ten rabbits having levels of 1.0 mg. antibody N per ml. serum or more, only four showed fatal reactions; one negative and two one plus reactions were obtained. Jackson further found that the amount of antigen necessary for fatal anaphylaxis was not decisive. In four of the eight rabbits dying of anaphylaxis, insufficient antigen to remove all of the circulating antibody was used while nineteen of twenty-one rabbits which failed to die in anaphylaxis received injections of egg albumin sufficient to remove all of the circulating antibody. In the rabbit, factors other than the quantities of antibody appear to be of importance in determining the outcome of anaphylactic shock.¹⁵

At about the same time Culbertson¹⁶ studied the severity of the Arthus phenomenon in rabbits actively immunized with crystalline egg albumin as a function of the amounts of anti-egg albumin in the circulation. As the level of circulating antibody rose following the last injection of antigen, the Arthus reaction tested on successive days became of increasing severity. With levels of circulating antibody of 0.08 mg. N per ml. or less, only mild reactions occurred, characterized by transient erythema and superficial scaling, while with levels of 0.12 to 0.16 mg. antibody N per ml. a slough was invariably obtained. When animals were allowed to rest until antibody was no longer demonstrable in their circulation, the Arthus reaction became negative. Similarly, negative reactions could be obtained temporarily by complete removal of antibody from the circulation by intravenous injection of sufficient antigen; upon reappearance of antibody positive Arthus tests again occurred.¹⁶

Culbertson¹⁶ was also the first to elicit the Arthus phenomenon passively with known amounts of antibody nitrogen. Injection of 0.047 mg. of egg albumin N intracutaneously into a rabbit one-half

hour after the animals had received an intravenous injection of 15 mg. of anti-egg albumin N resulted in a strongly positive Arthus reaction with a marked slough. Arthus reactions characterized by erythema and edema but with no slough resulted from intracutaneous injection of 0.75 and 0.075 mg. anti-egg albumin N followed one-half hour later by 0.047 mg. of egg albumin N. A reversed Arthus reaction consisting of erythema, edema and necrosis resulted from intravenous injection of about 10 mg. of egg albumin N followed by intracutaneous injection of 0.38 mg. of anti-egg albumin N. In all instances absorption of the antibody from the serum with antigen prior to injection abolished its capacity to produce an Arthus reaction.¹⁶

While these two earlier studies clearly demonstrate the superiority of studying allergic reactions in terms of the actual quantities of antibody and antigen involved, they did not provide sufficient data to establish the minimum quantities of antigen and antibody required for these reactions.

Further studies along these lines have been carried out in the writer's laboratory. In a study on passive anaphylaxis with Landow,¹⁷ the minimum quantities of rabbit anti-egg albumin (Ea) N or rabbit anti-SIII N (antibody to the specific polysaccharide of the type III pneumococcus) were determined which were required to sensitize a 250 Gm. guinea pig so that uniformly fatal anaphylactic shock would result on subsequent injection of a given amount of Ea N or of SIII forty-eight hours later. Both sensitizing and shocking doses were given intravenously. The antisera were analyzed for antibody N by the quantitative precipitin method and dilutions of antiserum containing the desired quantities of antibody were injected. From Table II it is seen that sensitization with about 0.03 mg. of anti-Ea N or anti-SIII N is sufficient to produce uniformly fatal anaphylactic shock when followed by a subsequent intravenous injection of 0.16 mg. Ea N or 0.10 mg. SIII, respectively. With sensitizing levels of 0.006 to 0.025 mg. antibody N anaphylactic

symptoms are usually observed but fatal reactions do not always occur. With even smaller quantities of antibody, none of the animals die and some may even fail to show symptoms of anaphylaxis.

Since these data represented passive

TABLE II
PASSIVE SENSITIZATION OF GUINEA PIGS WITH VARYING AMOUNTS OF RABBIT ANTIBODY*

Antibody N Injected	No. of Guinea Pigs Used	Results			
		Deaths	Severe Reac- tions	Slight Reac- tions	No Reac- tions
Rabbit anti-egg albumin—guinea pigs shocked with 1 mg. egg-albumin intravenously 48 hours after sensitizing injection					
mg.					
0.0019	4	0	0	2	2
0.0038	4	0	1	3	
0.0057	5	0	3	2	
0.0064	1	1			
0.0075	4	0	3	1	
0.0113	6	4	2		
0.023; 0.024	5	3	2		
0.034; 0.036	6	6			
0.048	2	2			
0.06	8	8			
0.072	1	1			
Rabbit antibody to type III pneumococcus—guinea pigs shocked with 0.1 mg. type III polysaccharide intra- venously 48 hours after sensitizing injection					
0.01	4	1	2	1	
0.02	5	4	1		
0.03	4	4			
0.04	4	4			

* From Kabat and Landow.¹⁷

sensitization of guinea pigs with serum of another species, a similar study was carried out with anti-Ea produced in the guinea pig.¹⁸ Since the guinea pig does not readily give rise to sufficient amounts of precipitin by the usual method of immunization, the Freund adjuvant technic¹⁹ was employed. As shown in Table III, guinea-pig anti-Ea N was equally effective as rabbit anti-Ea N in passive sensitization. This finding makes it probable that, in sensitization

with heterologous sera, the non-antibody protein injected together with the antibody does not affect its sensitizing capacity although it has been well established that a previous injection of serum of a foreign species inhibits anaphylactic shock.⁸

TABLE III
PASSIVE SENSITIZATION OF GUINEA PIGS WITH VARYING
AMOUNTS OF GUINEA PIG ANTI-OVALBUMIN—GUINEA
PIGS SHOCKED WITH 1 MG. OVALBUMIN INTRA-
VENOUSLY 48 HOURS AFTER SENSITIZING INJECTION *

Anti- body N In- jected Mg.	No. of Guinea Pigs Used	Results				
		Dead	Severe	Mod- erate	Slight	Nega- tive
0.005	6	..	2	2	2	
0.006	4	.	3	1		
0.010	7	5	2			
0.012	4	1	2	1		
0.015	7	6	1			
0.018	4	4				
0.020	8	7	1			
0.024	5	3	2			
0.030	8	8				
0.036	4	4				
0.040	10	10				
0.048	3	3				

* From Kabat and Boldt.¹⁸

In a more extensive study of passive anaphylaxis,²⁰ the severity of anaphylactic shock produced by varying quantities of antigen was studied at several sensitizing levels of antibody nitrogen. In the egg albumin rabbit anti-egg albumin system, it was found (Table iv) that an increase in the sensitizing dose from 0.03 to 0.15 mg. antibody N did not significantly change the quantity of antigen required to kill one-half of the animals; a further increase to 0.75 mg. antibody N, however, resulted in a five-fold increase in the antigen needed to produce 50 per cent anaphylactic deaths. In the SIII-anti-SIII system, however, similar variation in the sensitizing dose did not appear significantly to affect the quantity of antigen required for 50 per cent mortality. (Table iv.)

With tobacco mosaic virus and its homo-

logous rabbit antibody, fatal anaphylaxis could be obtained in guinea pigs sensitized with 0.03 mg. of antibody N only when the shocking dose was increased to 3.6 mg. N, many times more than was needed in the Ea-anti-Ea system. This is most reasonably ascribed to the higher molecular weight of tobacco mosaic virus (33,000,000) as compared with egg albumin (40,000) from which it follows that an equal weight of virus would contain many fewer molecules than would egg albumin. It is also in accord with the finding that the ratio of antibody N/antigen N at the point of maximum precipitation is about twenty times greater in the ovalbumin system than in the tobacco mosaic virus system.

Follensby and Hooker²¹ reported that four of six guinea pigs sensitized with 0.12 to 0.48 mg. rabbit anti-hemocyanin suffered fatal anaphylactic shock on injection of ten to forty-seven times the quantity of antigen optimal *in vitro* for complete precipitation of the antibody in the sensitizing dose; of the remaining animals one showed severe and the other mild anaphylaxis.

The quantitative relations in passive anaphylaxis have also been studied for a cross-reaction—the reaction between S VIII and rabbit anti-SIII.²⁰ In this system the amount of cross-reacting antibody N was determined and dilutions of antiserum containing known quantities of cross-reacting antibody N were injected. It is evident from Table iv that on sensitization with 0.03 mg. of cross-reacting antibody N, fatal anaphylactic shock could not be obtained, as it was in the homologous reaction, even when the antigen was varied from 0.005 to 4.0 mg. With larger sensitizing doses of antibody N, reactions of increasing severity were obtained with a shocking dose of 0.10 mg. of S VIII and uniformly fatal anaphylactic shock was found with 0.20 and 0.35 mg. cross-reacting antibody N. These results are in accord with quantitative precipitin studies on this system^{22,23} in which the cross-reaction was found to involve fewer reactive groups on the antibody molecule than did the homologous reaction.

TABLE IV

QUANTITATIVE RELATIONSHIPS BETWEEN AMOUNTS OF ANTIBODY AND ANTIGEN USED AND THE SEVERITY OF PASSIVE ANAPHYLAXIS IN THE GUINEA PIG*

Antibody N Injected for Sensitization Mg.	Antigen Injected to Elicit Shock									Approximate Amount of Antigen to Produce 50 Per Cent Mortality,† Mg. N
	0.16 Mg. N	0.12 Mg. N	0.08 Mg. N	0.04 Mg. N	0.02 Mg. N	0.01 Mg. N	0.0075 Mg. N	0.005 Mg. N	0.001 Mg. N	
Ovalbumin Rabbit Anti-Ovalbumin										
0.030	6 dead	3 dead 2 severe	4 dead† 1 severe	3 dead	9 dead	3 dead 1 severe 1 moderate 1 slight	4 dead 2 severe 1 moderate	0.007	
0.15	4 dead	3 dead	6 dead	7 dead	6 dead 1 severe 1 moderate	2 dead 6 severe 2 moderate 1 slight	1 dead 2 moderate 3 slight 1 negative	0.008	
0.75	3 dead	2 dead	6 dead	2 dead 1 severe 1 moderate	1 dead 1 severe 2 moderate 2 slight 1 negative 1 slight	0.04	
Tobacco Mosaic Virus Rabbit Anti-tobacco Mosaic Virus										
0.030	2 dead	1 severe	1 moderate	2 moderate					
0.10	1 dead	1 moderate	1 severe	1 slight					
0.20	1 slight	1 severe	2 slight§	1 slight					
SIII Rabbit Anti-SIII										
0.030	7 dead	7 dead	7 dead 1 severe	6 dead 1 severe	1 dead 2 severe 1 moderate	4 dead 2 severe	2 dead 1 severe 1 moderate	1 moderate 1 slight 2 negative	0.008
0.15	4 dead	5 dead	16 dead	6 dead 5 severe 1 moderate 2 slight	1 severe 1 moderate 1 slight 2 negative	1 moderate 1 slight 5 negative	0.005
0.75	2 dead	7 dead	2 severe 2 slight 1 negative	2 dead 1 severe	1 dead 2 moderate	2 slight 2 negative	0.01±
Cross Reacting Antibody N Injected for Sensitization										
4.0 Mg.	3.5 Mg.	2.0 Mg.	1.0 Mg.	0.50 Mg.	0.40 Mg.	0.20 Mg.	0.10 Mg.	0.005 Mg.		
SVIII Rabbit Anti-SIII										
0.030	1 moderate	1 moderate	2 slight	1 moderate 1 slight	1 severe 1 moderate 1 slight	2 doubtful 2 negative	2 slight 1 doubtful	
0.050	1 dead 1 moderate	2 severe 1 moderate	4 severe	2 negative	
0.060	2 dead 2 severe	1 dead 1 severe 1 moderate 1 slight	1 dead 1 severe 1 moderate 1 slight	
0.10	6 dead	3 dead 3 severe 1 slight	3 dead 3 severe 1 slight	
0.20	5 dead	5 dead	
0.35	4 dead	4 dead	

* From Kabat, Coffin and Smith ²⁰

† Estimated by inspection; essentially similar results derived from statistical considerations.

‡ 1 delayed death.

§ 1 animal received 0.30 mg. antigen N.

|| Including data from (17).

Passive anaphylaxis studies with measured quantities of antibody nitrogen are especially useful in clearly establishing differences in the capacity of sera of various species to confer passive sensitivity. For instance, it is readily evident from the studies of Follensby and Hooker²¹ under what conditions passive sensitization of guinea pigs with equine anti-hemocyanin and equine anti-egg albumin could not be obtained; and it is conceivable that the finding of Bailey and co-workers^{24,25} that guinea pigs could be passively sensitized with horse anti-pneumococcal antibody, which appear to be contradicted by the studies of all other workers,²⁶⁻²⁸ might be explained by differences in the quantities of antibody N used by the various workers for sensitization. If known quantities of antibody N were used in standardization of passive anaphylaxis for estimating small amounts of polysaccharides as proposed by Morgan,²⁹ this would also serve to ensure reproducibility between different laboratories and with different lots of sera. These standardized conditions for passive anaphylaxis have also proved of value in studying the effects of various unrelated substances on anaphylaxis. For instance, Coffin and Kabat³⁰ used this procedure in demonstrating that immunization with histamine azoprotein or with normal human serum protects guinea pigs against fatal anaphylactic shock indicating that the protection was not specific for histamine azoprotein.

Quantitative studies have also provided an estimate of the weights of antibody which must be present in isolated muscle tissue for anaphylactic contractions to occur. Studies on isolated uterine horns of a limited number of female guinea pigs sensitized by injection of known quantities of anti-EaN showed that, on addition of 0.16 mg. EaN to the bath, good contractions were obtained in two animals sensitized with 0.03 mg. antibody N, in one of two sensitized with 0.02 mg. antibody N and in one of three sensitized with 0.01 mg. antibody N. These findings suggest that the sensitivity of the isolated guinea pig uterus

is of the same order as that of the intact animal.¹⁹ If the intravenously injected anti-EaN is uniformly distributed throughout the tissues of the guinea pig, as appears reasonable from Freund's studies,³¹⁻³⁴ a contracting guinea pig uterine horn (wt. 75 mg.) would contain only 0.01 μ g. antibody N of the 30 μ g. antibody N injected into the 250 Gm. guinea pig. This quantity of antibody N is considerably less than can be detected by *in vitro* serologic tests and may perhaps provide an explanation for the failure of the sera of hypersensitive patients to give the usual serologic tests for antibody.

Additional information on the conditions under which anaphylactic shock occurs in the guinea pig may be obtained by bleeding guinea pigs injected with known quantities of antibody N at the time when the shocking dose of antigen would ordinarily be given and determining the amount of circulating antibody by the micro-quantitative precipitin method^{11-13,35} after removal of complement.³⁶ Data of this kind have been obtained for the Ea-anti Ea and SIII-anti SIII systems.²⁰ Table v shows the quantities of antibody N in the circulation forty-eight hours after 30, 150, and 750 μ g. anti-EaN or anti-SIII N were injected into guinea pigs. With anti-Ea, it is evident that significant quantities of circulating antibody did not remain in the circulation when 30 or 150 μ g. anti-EaN was injected but that a considerable proportion of the total antibody was present in the blood forty-eight hours after 750 μ g. anti-EaN were given. By comparison with the data in Table iv, it would appear that the increased quantity of antigen required to kill one-half of the guinea pigs sensitized with 750 μ g. anti-EaN might be attributed to a protective effect of circulating antibody. In the SIII-anti SIII system, however, about 30 to 50 per cent of the injected antibody remained in the circulation at the time of shock and no evidence of a significant increase in the shocking dose of SIII was found. (Table iv.) The reasons for the apparent protective action of circulating antibody in the

Ea-anti Ea system and the absence of such an effect in the SIII-anti SIII system require further investigation.

Quantitative data have also been obtained relating the severity of the Arthus reaction, induced passively in the rabbit,

anti-EaN and the severity of the reaction increased with the quantity of antibody. (Table VI.) With animals sensitized intracutaneously with antibody, the reaction was of comparable degree even if antigen was given intravenously and no significant

TABLE V
RELATION BETWEEN ANTIBODY NITROGEN INJECTED INTRAVENOUSLY INTO GUINEA PIGS AND THE QUANTITY IN THE SERUM 48 HOURS LATER*

Guinea Pig	Serum Volume,† Ml.	Antibody N Injected Intravenously, µg.	Antibody N in Serum 48 Hours Later, µg./ml.	Total Circulating Antibody N 48 Hours Later, µg.	Guinea Pig	Serum Volume,† Ml.	Antibody N Injected Intravenously, µg.	Antibody N in Serum 48 Hours Later, µg./ml.	Total Circulating Antibody N 48 Hours Later, µg.
Rabbit anti-egg albumin					Rabbit antibody to pneumococcal polysaccharide, type III				
1	11	30	0.0	0	21	10.5	30	1.0‡	10.5‡
2	11	30	0.0	0	22	9	30	1.2‡	11‡
3	8	30	0.0	0	23	10	30	0	0
4	8	30	0.0	0	27	9.5	30	2.3§	22
5	8	30	0.6‡	5‡	28	10	30	0.6‡	6‡
6	10	150	0.4‡	4‡	17	10	150	7.5	75
7	12	150	0.9‡	11‡	18	11	150	4.0	44
9	11	150	1.3‡	14‡	19	11.5	150	6.4	74
15	13	150	0.8‡	10‡	20	12	150	4.2	50
10	8.5	750	17.6	150	24	9	750	28.5	255
11	10.5	750	2.5	25	25	9.5	750	32.0	305
12	11	750	29.0	320	26	9.5	750	24.2	230
13	9	750	33.0	300					
14	8	750	3.9	30					
29	10.5	750	14.9	155					
30	11	750	5.1	55					

* From Kabat, Coffin and Smith.²⁰

† $\frac{1}{2}$ of body weight taken to the nearest 0.5 ml.

‡ Values of less than 1–2 µg. N/ml. are within experimental error.

§ One determination lost.

to the quantities of EaN and anti-EaN.³⁷ After preliminary experiments, the interval of one-half hour between the sensitizing and shocking doses, as employed by Culbertson,¹⁶ was adopted as most satisfactory. When the antibody and antigen were administered intracutaneously, it was found that the severity of the reaction was determined primarily by the quantity of antibody and was rather insensitive to the amount of antigen once a threshold quantity was exceeded. Minimal Arthus reactions were obtained by local injection of 0.025 mg.

differences in the intensity of the responses were observed with reversed³⁸ as compared with direct local Arthus reactions. (Table VI.)

When the antibody was administered intravenously and the antigen locally, considerably larger amounts of antibody were required for a minimal Arthus response. In only one of two rabbits which received 1.12 mg. anti-EaN intravenously could a minimal Arthus reaction be elicited. With two and four times this quantity of antibody N, reactions increasing in intensity

resulted. Culbertson¹⁶ was able to produce a slough by intravenous injection of 15 mg. anti-EaN.

The passive Arthus phenomenon in the rabbit, therefore, appears to differ sharply from passive anaphylaxis in the guinea pig.

as much, to contract on addition of antigen. Even if these values are corrected for the different weights of tissue participating, induction of the Arthus reaction clearly requires many times more antibody than does local anaphylactic shock.

TABLE VI
RELATIONSHIP BETWEEN SENSITIZING AND SHOCK DOSES ON SEVERITY OF THE PASSIVELY INDUCED ARTHUS REACTION IN LOCALLY SENSITIZED RABBITS*

Anti-egg Albumin Nitrogen Mg.	Egg Albumin Nitrogen, Mg.										
	0.5	0.25	0.13	0.06	0.03	0.015	0.008	0.004	0.001	0.0005	0.0001
0.9	++++	++++	++++ ++++ ++++ ++++	+++							
0.67	++++ ++++ ++++ ++++								
0.45	++++ <div>+++</div>	++++ ++++ ++++ <div>+++</div>	+++ <div>++++</div>	+++ <div>++++</div>	+++ <div>+++</div>	± <div>+++</div>	± <div>++</div>	0
0.22	++++	++++ ++++ +++	++++ ++++ ++++ +++	++++ ++++ +++ <div>++</div>	+++ <div>++</div>	+++ <div>++</div>	++ ++ ++ <div>+</div>	++ ++ <div>+</div>	0 <div>+</div>
0.15	+++ ++	+++ ++	+++ +++ +++ <div>++</div>	+++ +++ +++ <div>++</div>	+++ +++ +++ <div>++</div>	+++ +++ +++ <div>++</div>	<div>++</div>	<div>++</div>	
0.10	+++ ++	+++ ++	+++ +++ ++	+++ +++ ++	+++ +++ ++	+++ +++ ++	
0.05	++ ++ <div>+++</div>	++ +	++ ++ <div>+</div>	++ ++ <div>++</div>	++ ++ <div>++</div>	++ ++ <div>++</div>	++ ++ <div>+</div>	± <div>+</div>	
0.025	++ + <div>+</div>	++ +	++ ++ <div>+</div>	++ ++ <div>++</div>	++ ++ <div>++</div>	++ ++ <div>++</div>	++ ++ ++ ± +	++ <div>+</div>	± <div>+</div>	0 <div>0</div>
0.01	0 0 <div>0</div>	0 0 <div>0</div>	0 0 <div>±</div>	0 0 <div>0</div>	0 0 <div>0</div>	0 0 <div>0</div> <div>+</div>	± <div>+</div>	± <div>+</div>	0 <div>0</div>

*From Fischel and Kabat.³⁷

In the former instance, 25 μ g. of antibody N was required for a minimal local reaction while it was calculated that a strip of guinea pig uterine muscle need contain about 0.01 μ g. antibody N, or only $\frac{1}{2500}$

Thus far, anaphylaxis and the Arthus phenomenon are the only allergic reactions for which quantitative data are available. It should not be too difficult to extend these studies to at least several other allergic

manifestations and to compare the amounts of antigen and antibody required to elicit these reactions in different species. The finding of Mehlman and Seegal²⁷ that horse antibody to the pneumococcal polysaccharides, while not conferring anaphylactic sensitivity, would sensitize so that a wheal and erythema type of response would be induced in the guinea pig on subsequent injection of polysaccharide deserves such quantitative treatment; and the subsequent report by Mehlman³⁸ that passive anaphylaxis could be induced in dogs sensitized with horse or rabbit anti-pneumococcal serum also merits quantitative study. Indeed, quantitative studies on the sensitizing properties of the antibodies produced in guinea pigs and rabbits with low molecular weight simple substances, such as citraconic anhydride³⁹ and others,^{39,40} might further broaden our concepts to include the drug allergies.

The most severe limitation to the extension of this approach to the study of the quantitative aspects of human allergic reactions is the complex nature of the antigenic mixtures used in testing for hypersensitivity and failure thus far to find any *in vitro* reactions of antibodies which are amenable to quantitative immunochemical study in the sera of individuals with the common allergies. It is possible that as more sensitive immunochemical methods of measuring antibody are developed *in vitro* tests may be obtained. Perhaps the study of the sera of individuals sensitive to horse serum will prove of value in this connection; in one such serum quantitative measurements of precipitin have recently been made.⁴¹ In any event, a comprehensive picture of the quantitative aspects of the various allergic reactions in different animal species should serve as a convenient framework within which much of our knowledge can be coordinated.

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Rôle of Histamine in Anaphylaxis and Allergy*

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IT was recognized early in the study of anaphylaxis that the symptoms produced by the injection of a foreign protein into a previously sensitized animal could best be explained on the basis of an explosive release of some toxic substance. Following the isolation of histamine from ergot,¹ Dale and Laidlaw² came to the conclusion that its pharmacologic effects in animals closely resembled those observed in anaphylactic shock and ventured the opinion that histamine might indeed be released in the latter phenomenon. When histamine was shown to be a normal constituent of tissues,³ this possibility seemed even more likely and, in 1927, Dale⁴ proposed the theory that histamine is liberated from the tissues of animals by cell stimulation resulting from the interaction of antigen with antibody. He was careful to point out that histamine existed in cells as such and was released not formed by this mechanism. In 1908, Von Pirquet⁵ emphasized the close relationship between anaphylaxis and allergy and, in 1927, Sir Thomas Lewis⁶ published his now classical observations on the triple response and H- or histamine-like substance.

So great was the impetus to clarify this whole subject that a relatively enormous literature has grown and many reviews on the subject have appeared, the most recent being those by Feldberg,⁷ Dragstedt,⁸ Code,⁹ Rocha e Silva,¹⁰ Selle,¹¹ Rose,¹² and Feinberg.¹³ The present review is an attempt to consider some of the recent work on this subject as well as certain aspects of histamine metabolism which may be pertinent to the discussion as a whole. In this connection,

two facts should be borne in mind: The first is that relatively little is known of the physiologic significance of histamine and the second is that most of our knowledge of its activity in allergic states is of an indirect nature. Practically all of the investigations which have been made rely on a biologic method of assay; and while it is generally agreed that histamine as such is being estimated, final proof must await chemical identification.

METABOLISM

Histamine is derived from histidine, one of the essential amino acids, by decarboxylation. In support of this, Anrep et al.¹⁴ were able to demonstrate an increase in the histamine excretion in the urine of patients to whom food was fed that was high in histidine. Normally, however, it is probable that this breakdown occurs in the intestine by the action of suitable bacteria. Histamine may be excreted, apparently unchanged, in the urine or inactivated by histaminase, an enzyme first isolated by Best¹⁵ from lung tissue. It may also be inactivated by tissues which do not contain histaminase such as the kidney and liver of the rat.¹⁶ The metabolism of histamine is under the influence of certain endocrine glands. Rose and Browne²⁰ noted an increase in the histamine content of the tissues of the rat following removal of the adrenal glands and this was confirmed by Marshall.²¹ The histamine content of the blood is also increased in both the rat²¹ and rabbit²² under these conditions. According to Gotzl and Dragstedt,²³ thyroidectomy results in a decrease of the histamine content of the skin

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and tissues of the rat whereas the administration of thyroid extracts increases its content in these tissues. It is of interest to note that removal of these glands results in a decreased resistance to histamine^{24,25} as well as to anaphylactic shock.²⁶⁻²⁸

DISTRIBUTION IN TISSUES

Histamine has been isolated in the crystalline state from animal tissues by Best, Dale, Dudley and Thorpe³ and, more recently, by Code and Ing²⁹ from the blood of the rabbit. Using various biologic methods of assay, it has been shown to be present in most animal tissues but predominantly in the so-called "shock" tissues such as the lungs of the guinea pig and the liver of the dog. In the mouse over 60 per cent is found in the skin.³⁰ The blood of most animals contains histamine, the highest amount being found in the rabbit and the lowest in the cat.³¹ In man, using Code's modification³² of Barsoum and Gaddum's method,³³ most workers have found the blood histamine content to vary from 2 to 7 γ /100 cc. expressed as base.³⁴⁻³⁶ It is also present in small amounts in cerebrospinal fluid.³⁷ In a study of the histamine content of gastric mucosa in man Trach, Code and Wangenstein³⁸ found an average of 10.2 mg. per Kg. in the antral portion and 5.8 mg./Kg. in the fundus. Pellerat¹⁷ has recently shown that the histamine content of the skin of normal man varies from 16 to 24 mg./Kg. Although the tissue of the central nervous system is virtually devoid of histamine, Kwiatkowski³⁹ found it to be present in large amounts in the peripheral sensory nerves. It is of interest that these are the only nerves capable of antidromic stimulation.

Of great importance, however, is the disposition of this histamine. Like other metabolites, such as potassium, the major portion of blood or tissue histamine is either bound to or held within the cell. It was first demonstrated by Code,⁴⁰ and later confirmed by others,⁴⁰⁻⁴² that 70 to 90 per cent of the blood histamine is held in an inactive state within the white blood cell elements, the small remainder circulating

in a free state in the plasma or held within the red blood corpuscles. Tissue histamine, such as that of the lungs or liver, is held in a similar manner within the tissue cells.^{43,44} It will be obvious, therefore, that in this bound and inactive form histamine constitutes a ready source of a powerful toxic substance capable of instant action on release.

PHYSIOLOGY AND PHARMACOLOGY

It is not known what rôle histamine may play in the economy of the organism. From the evidence at hand it seems likely that along with other vasodilator substances it forms part of the control mechanism of the circulation, balancing the action of vasoconstrictor substances such as adrenalin. In support of this concept, Feldberg⁴⁵ as well as others⁴⁶ have shown that the injection of histamine will stimulate the release of adrenalin from the medulla of the adrenal gland. Furthermore, Staub⁴⁷ has demonstrated that the intravenous injection of adrenalin in man will produce an increase of the histamine content of the blood plasma. Since plasma histamine is active, Staub⁴⁸ suggests that this reciprocal relationship is part of the regulatory mechanism of the circulation. It is believed by some that the secretion of hydrochloric acid by the gastric mucosa may be mediated by histamine.⁴⁹ While there is no conclusive evidence to support this theory, McGavack et al.⁵⁰ were able to suppress completely hydrochloric acid secretion in man by three to four weeks administration of benadryl, an antihistamine substance, in high dosage.

Pharmacologic studies on the actions of histamine are countless, for there is hardly an organ or tissue which will not respond in some way to this substance. For the present purpose, however, it will suffice to remember its four main properties. These are, that it produces contraction of smooth muscle, that it produces dilatation of capillaries and venules in most species and, in man, the arterioles as well, that it markedly increases capillary permeability and that it is a potent stimulator of glandular secretion. It will become apparent immediately that

these properties could account for many of the symptoms and signs of anaphylaxis as well as those of allergy. In the latter, the constriction of the bronchioles and secretion of mucus is prominent in asthma. Dilatation and increased permeability of the capillaries are the basic changes in urticaria as well as those seen in vasomotor rhinitis. Similarly, in anaphylactic shock in most animal species the major changes observed may be reproduced by the administration of histamine and, as previously pointed out, it was this similarity in action of the two conditions, namely, histamine intoxication and anaphylactic shock, which led Dale to formulate the theory of histamine as the mediator of anaphylaxis and allergic symptoms. Yet, as will be discussed later, there is increasing evidence that other factors must play a rôle as well.

METHODS OF DETERMINATION

The original method of Barsoum and Gaddum,³³ as modified by Code,³² has been used by the majority of recent investigators for the determination of histamine in blood and tissue. It is assumed that histamine as such, whether in the free or bound form, is being extracted. Some doubt has been cast on this assumption by the recent work of Rocha e Silva,⁵¹ who has made use of chemical combinations of histamine bound to amino acids by peptide linkage. Pharmacologically, such compounds are inactive. Yet when they are subjected to the Code method of extraction, the histamine component is recovered quantitatively in an active form.¹⁰ It is possible, therefore, that the whole blood and tissue values, as determined by Code's method, are made up of inactive histamine bound to other amino acids as well as of free histamine itself. Furthermore, Pellerat¹⁷ claims to have shown that a smooth muscle contracting substance may be extracted from urine by the Code method in addition to histamine. This substance, which ordinarily would be regarded as histamine, can be distinguished by the fact that its activity is not inhibited by antihistamine compounds nor is it in-

activated by histaminase. How far these observations can be extended to results reported by others will have to await further confirmation. In this review, however, these histamine-like substances are referred to as histamine base, in gamma per 100 cc. of blood or other fluid or gamma per Kg. of tissue.

ANAPHYLAXIS

There can be no doubt that histamine plays a major rôle in the phenomenon of anaphylaxis in most animal species. However, it must be emphasized at the outset that the histamine theory does not pretend and never claimed to reduce all the manifestations of the antigen-antibody reaction to histamine effects.⁵³ The first demonstrations of histamine release as a result of antibody-antigen reaction were made independently in 1932. Bartosch, Feldberg and Nagel⁵⁴ showed the release of histamine from the isolated, perfused lungs of the sensitized guinea pig following addition of the specific antigen to the perfusing solution. Dragstedt and Gebauer-Fuellnegg⁵⁵ were successful in demonstrating large amounts of histamine in the blood and lymph of the dog rendered anaphylactic. It was not, however, until 1939 that Code⁵⁶ recorded the quantitative release of histamine into the blood of these two species thus firmly establishing histamine as a major factor in the production of symptoms and clarifying the sequence of events.

A consideration of anaphylaxis in relation to the histamine theory still leaves certain discrepancies unanswered. The guinea pig, perhaps of all animal species investigated, has until recently fulfilled most criteria. Thus, Code⁵⁶ established that sufficient histamine is liberated during fatal guinea pig anaphylaxis to account for the death of that animal. Many workers have shown that this species can be protected to a high degree by previous administration of antihistamine compounds.^{13, 57, 58} However, it is notable that although antihistamine compounds vary markedly in their antihistamine activity some such as neo-antergan being much more potent than others

such as benadryl, the same dose of either compound affords protection against anaphylactic shock.^{13,58} Again, while the administration of pyribenzamine by aerosol inhalation will protect a large percentage of guinea pigs from the immediate effects of induced anaphylactic shock, Mayer, Brousseau and Eisman⁵⁹ remark on the fact that some animals die within twenty-four hours apparently from some other cause. The same dose of pyribenzamine will completely protect these animals against fifteen lethal doses of histamine. The administration of papaverine, while able to protect 53 per cent of guinea pigs from anaphylactic shock, afforded no protection against histamine shock.⁶⁰ It is thus apparent that other mechanisms beside histamine release must be participating in this phenomenon. Of considerable interest in this connection is heterophile anaphylaxis. When this antigen-antibody response is produced in the guinea pig with resulting fatal shock, there is no release of histamine into the blood.⁶¹ It should be pointed out that heterophile anaphylaxis is the reverse, in a sense, of foreign protein anaphylaxis and the tissues exhibit signs of greater damage as a rule. However, it is still an antigen-antibody reaction even though in this case the antibody is injected into the guinea pig which possesses naturally occurring antigen.⁶² Thus, here is a form of anaphylaxis which seems at present to bear little if any relation to histamine release. It would be interesting to determine the effect of antihistamine derivatives on this reaction.

There is much evidence which supports the theory of histamine release in canine anaphylaxis. In this species, Code⁵⁶ has shown that not only is there a marked and explosive increase of the blood histamine but that the major portion is released into the plasma where it is free to exert its characteristic actions. However, if one examines the charts published by Code in his paper on anaphylaxis in the dog, it will be observed that while there is a rapid release of this compound which seems to bear a definite relation to the degree of shock occurring in

the early stages, profound shock leading to coma and death in the later stages was observed in the presence of a normal blood histamine. Commenting on this in a later review, Code states,⁹ "While histamine seems quite clearly to be the cause of death in the early stages of the reaction, there is some difficulty in incriminating it as the lethal factor when its presence can barely be detected in the blood."²

The liver has been regarded as the major site of histamine release in the dog; it has been shown by Ojers, Holmes and Dragstedt⁶³ that the histamine content of this organ decreases following the production of anaphylaxis in the intact dog. It is also the site of heparin release as demonstrated by Jaques and Waters in 1941.⁶⁴ However, it is probable that other tissues participate in the reaction as well for anaphylaxis has been produced in dogs with an Eck fistula⁶⁵ as well as in dogs from which the liver has been removed entirely.⁶⁶

Finally, in this species histamine and anaphylactic shock can be prevented in large measure by the previous administration of antihistamine compounds.⁶⁷⁻⁶⁹ Here again, however, certain discrepancies have been observed. In their observations on pyribenzamine, Yonkman, Oppenheimer et al.⁷⁰ noted that, whereas this antihistamine compound prevents histamine-induced bronchiolar constriction in isolated dog lung, the constriction produced by adding antigen to the fluid perfusing isolated lung from a dog previously sensitized was not inhibited. Bronchoconstriction is not a feature; however, of *in vivo* anaphylaxis.

Turning now to the rabbit, one is faced with an apparent reversal of events. It was first demonstrated by Rose and Weil,⁷¹ and later confirmed by others,^{72,73} that acute anaphylaxis in this species was accompanied by a drastic decrease in the blood histamine. Furthermore, no consistent increase could be detected in the active plasma histamine. However, the fundamental reaction, namely, release of histamine from cells by antigen-antibody combination, was demonstrated by Katz.⁷⁴ Upon the addition of horse

serum to the blood of a rabbit sensitized to this substance, he was able to show that histamine was liberated from the cells into the plasma. This observation, which was confirmed,⁷⁵ was then taken as evidence by Dragstedt⁷⁶ that histamine plays an active rôle in rabbit anaphylaxis. Dragstedt and his co-workers⁷² found that on addition of antigen to blood, which was perfused through the isolated lungs of a sensitized rabbit, histamine was removed from the blood, presumably by the lungs. However, in further experiments, Rose⁷⁷ demonstrated that not only was the histamine content of the blood decreased during anaphylactic shock but also that of the tissues, particularly of the lung and spleen. It is perhaps pertinent to note that a marked decrease in the blood histamine of the rabbit can be produced by the injection of glycogen.⁷⁸ No evidence of shock accompanies this phenomenon, however, and it is probable that the histamine is taken up in part by the lungs since there is a marked thrombocytopenia at the same time. Providing such histamine remains in the combined or intracellular form in which it is inactive, no effects are produced. This is borne out by the fact that addition of glycogen to rabbit blood *in vitro* does not release histamine from the cells into the plasma.⁷⁸ Thus, it appears reasonably clear, as emphasized by Dragstedt,⁷⁶ that the fundamental phenomenon in rabbit anaphylaxis again is a liberation of histamine from cells into the plasma. It yet remains to be shown, however, whether antihistamine compounds are capable of inhibiting rabbit anaphylaxis.

In the mouse, anaphylactic shock can readily be produced.⁷⁹ In a comparative study on anaphylaxis and histamine intoxication in this species, Perry and Darsie⁸⁰ found that while fatal anaphylaxis could readily be induced the animals were quite refractory to histamine intoxication when a dose of approximately 400 mg./Kg. was administered intravenously. Mayer and Brousseau⁸¹ studied the effect of pyribenzamine on these two conditions in the mouse. In controls, the injection of 500 mg. of

histamine per body weight killed 50 per cent of the animals used. If either pyribenzamine or benadryl were administered in adequate dosage (10 to 25 mg./Kg.) fifteen minutes before the injection of histamine was made, contrary to expectations, the effect of histamine was enhanced and a dose of 375 mg./Kg. killed 100 per cent. In the mice rendered anaphylactic, on the other hand, some degree of protection was afforded. Both these authors therefore conclude that anaphylaxis in this species is not based on histamine release. Mayer and Brousseau⁸¹ explain their results in histamine poisoning by regarding histamine and the antihistamine compounds as two separate toxins each acting independently. Thus, the toxic action of pyribenzamine or benadryl decreases the amount of histamine required to kill the animals. They further explain the protective action of pyribenzamine in mouse anaphylaxis on some other unknown pharmacologic property of this compound. If one is to consider pyribenzamine as an inhibitor of anaphylactic shock in the mouse on some basis other than its antihistamine property, it is possible that anaphylaxis in other species may in part be inhibited by these antihistamine compounds in a similar way. This may in turn provide some explanation for the disparity between their antianaphylactic and antihistaminic activity. One may conclude from these observations that in all probability the release of histamine is not a factor in this form of anaphylaxis. It may be of interest here to refer to the experiments of Dekanski.³⁰ He has demonstrated a 100 per cent increase in the histamine content of the skin of the mouse following scalding. Apparently, this excess histamine is formed, not released, as a result of the injury. It would be of interest to know whether any similar mechanism exists in mouse anaphylaxis.

While the rôle of histamine has not been investigated in rat anaphylaxis, it has been shown that thyroidectomy decreases; and the administration of thyroxin increases its susceptibility to anaphylactic shock.⁸² Simi-

lar results were obtained in the anaphylactoid reaction to a single injection of egg white in these animals.⁸² It is of interest to note that the latter condition can be inhibited by antihistamine compounds.⁸³

Finally, there remains the observations of Code and Hester,⁸⁴ who found that anaphylactic shock in the horse and calf is accompanied by a decrease in the blood histamine. Andberg, Boyd and Code⁸⁵ were able to show that the injection of histamine in the horse produces respiratory symptoms indistinguishable from those associated with acute anaphylaxis in this species. However, other features such as cough and bladder contraction were lacking.

MECHANISM OF HISTAMINE RELEASE FROM CELLS

The older theories of anaphylaxis suggested that the toxic manifestations of this phenomenon might be due to the formation of protein breakdown or cleavage products resulting from proteolytic activity. Although our concept has changed to the more modern one indicating that such a toxic substance must be released and not formed, recent observations would seem to indicate that proteolytic action may indeed play a major rôle in this process. Two theories have been proposed along these lines. In investigating the mechanism whereby venoms are able to liberate histamine from cells, Feldberg and Kellaway⁸⁶ found that lysolecithin, a hemolytic enzyme, was formed. They subsequently showed that its formation was responsible for the liberation of histamine from organs perfused with snake and bee venoms.⁸⁷⁻⁸⁹ It was argued that since cell structure is regarded as a complex of lipoprotein films⁹⁰ in which histamine is fixed a splitting of these lipins could account for histamine release. This assumption, however, would have to account for the fact that there is no evidence at present for the existence of a hemolytic effect in anaphylaxis, as pointed out by Feldberg.⁷

Another approach to the enzymatic theory has recently been reinvestigated by Rocha e Silva.⁹¹ In 1909, Biedl and Krause⁹²

emphasized the marked similarity between peptone shock and anaphylaxis. Lewis⁶ and Dale⁴ both suggested that protein breakdown might lead to the formation of peptone which in turn might initiate a release of histamine. The observations of Feldberg, Kellaway and O'Connor,⁹² and Dragstedt and his co-workers as well as of others, have clearly shown the remarkable similarity between the effects of peptone administration and anaphylaxis. Thus, in the intact dog the injection of peptone causes a release of histamine into the blood,⁹⁴ a decrease in the liver histamine,⁹⁵ an outpouring of heparin^{96,97} and a marked thrombocytopenia,⁹⁸ all of which occur in anaphylactic shock as well. Similarly, peptone administration in the rabbit causes a fall in blood histamine⁹⁹ and thrombocytopenia. Histamine, furthermore, is released from the white blood cells of the rabbit *in vitro* on addition of peptone.⁹⁹ All of these observations, therefore, amply strengthen the concept that the release of histamine and heparin from tissue cells, as well as the thrombocytopenia, are initiated by a similar mechanism in these two types of shock.

Other substances such as animal venoms were shown to produce effects markedly similar to anaphylactic shock as well as to release histamine when injected into animals.^{100,101} In considering these effects, Rocha e Silva¹⁰¹ concluded that this property could best be explained by the fact that these venoms contain a proteolytic enzyme similar to trypsin since trypsin itself was able to produce effects indistinguishable from those of venoms. Further investigation by Rocha e Silva¹⁰² and Arellano, Lawton and Dragstedt¹⁰³ showed that trypsin was capable of producing many of the alterations in blood histamine in different species similar to those occurring in peptone and anaphylactic shock.¹⁰³⁻¹⁰⁷ While there are definite discrepancies, such as the failure of trypsin to release histamine in the guinea pig,^{106,108} heparin in the intact dog¹⁰⁹ or the inability of benadryl to prevent the symptoms of trypsin shock in the dog or the guinea pig,¹¹⁰ Rocha e Silva believed

that the evidence was sufficient to warrant a further search for a trypsin-like enzyme in anaphylaxis.

Pursuing this idea, he and his co-workers demonstrated that in the isolated dog liver perfused with tyrode solution trypsin alone was capable of releasing histamine whereas peptone, ascaris extract or antigen required blood as the perfusing medium.^{105,113} Using blood preserved by the silicone method of Jaques et al.,¹¹¹ by means of which it may be kept from coagulating for several hours without deterioration of any of its constituents, relatively enormous quantities of histamine and heparin were released from the isolated liver on addition of peptone. These surprising results made it obvious that whereas trypsin, a proteolytic enzyme, is capable of releasing histamine and heparin from the isolated dog liver in the absence of blood the latter, or one of its constituents, is essential for the release of these substances when peptone, ascaris extracts or antigen (in the sensitized liver) is used.

The marked reduction in platelets and leukocytes which accompanies all these reactions both in the intact animal or when isolated liver is perfused with blood^{112,114,115} was taken as evidence of their participation in the mechanism of histamine release. By making stained smears of liver tissue the platelets could be demonstrated within the parenchyma. It was shown that the degree of disintegration of these elements bore some relation to the quantities of histamine and heparin released. Thus, in the earlier experiments when heparinized blood was used as the perfusing agent sometimes little or no histamine was released and the platelets were found intact. With silicone blood, the platelets were found to be disintegrated and there was an accompanying enormous release of histamine and heparin.^{91,112} Since platelets are known to contain kinase for plasma trypsin,¹¹⁶ Rocha e Silva and Texeira¹¹⁷ have formulated the theory that their disintegration activates a proteolytic enzyme, most probably trypsin, which in turn causes cell damage and release of metabolites such as histamine and heparin. In further

support of this attractive theory, Jaques, Rocha e Silva and Scroggie¹¹⁹ have demonstrated that plasma trypsin, or an enzyme like it, is activated in the dog liver perfused with silicone preserved blood to which peptone is added. Thus, fibrinolysis of the clot, which forms in the perfusate when protamine is added to inhibit the action of released heparin,¹¹⁷ was found to occur. Finally, soybean tryptic inhibitor which prevents the action of trypsin was also found to inhibit this fibrinolysis. Although these experiments have not been repeated for antigen-antibody reaction, they constitute a great step forward in our understanding of the mechanism of peptone shock in the dog and may shed more light on the mechanism of histamine release in anaphylaxis in other species.

Additional support of the theory that a tryptic ferment is responsible for histamine release has been furnished by Rocha e Silva.¹²⁰ He observed that papain, a mixture of proteolytic enzymes with some of the specific characteristics of animal cathepsins, is capable of releasing histamine by virtue of its ability to split benzoyl-L-argininamide. This is a specific substrate for cathepsin II¹²¹ as well as a typical one for trypsin. Rocha e Silva¹⁰ has therefore suggested that histamine is held in the cell forming an amide linkage with either lysine or arginine. Synthetic compounds of histamine, chemically bound to amino acids by a peptide linkage, were prepared and suggested as chemical models of tissue histamine. These compounds were pharmacologically inactive but upon acid hydrolysis which ruptured the peptide bond the amine was liberated in active form.¹²²

That protein breakdown occurs during anaphylactic shock in the dog has recently been shown by Miller.⁵² This cannot be regarded as a specific result of anaphylaxis for it is known to occur following many other forms of injury.^{123,124} Yet it supports the proteolytic theory of antigen-antibody combination. It is obvious, however, that by whatever basic mechanism histamine and other metabolites are released in an active

form in most types of anaphylactic shock. Whether a transient increase or decrease in the blood histamine occurs would seem to be less important and is simply an indication of shift of histamine from one locale to another. Of greater importance is whether during this shift it is released and how sensitive are the tissues with which it comes into contact. As will be pointed out, there is evidence to show that in the allergic or hypersensitive state certain tissues are much more reactive to histamine than when they are in the normal state.

As in many other aspects of physiology there are species differences in anaphylaxis. The fundamental reaction of a release of histamine from cells by the interaction of antigen with antibody has, for the most part, been substantiated. As Code⁹ rightly points out, the challenging problem is the damaged cell. While the injection of histamine may reproduce some of the symptoms of anaphylaxis, it is not capable of producing the morphologic changes which result from anaphylactic shock.⁷ If present, it is released along with other substances as a result of this damage. That histamine plays a major rôle in this syndrome is beyond question and, as will be seen in another section of this symposium, confirmatory evidence, although it is of an indirect nature, is ample through the effect of antihistamine compounds.

RÔLE OF HISTAMINE IN ALLERGY.

The basic factors involved in the mechanism of both allergy and anaphylaxis have led many to believe that they are manifestations of one and the same phenomenon. As will be seen, this aspect of the field has not kept abreast of the evidence for the participation of histamine in anaphylaxis.

At the outset, it should be remembered that whereas acute anaphylaxis is a general reaction in which many of the body tissues participate, allergic phenomena are usually confined to one or two specific tissues such as the mucosa of the upper respiratory tract, the bronchiolar musculature and glandular tissue or the skin. While it is possible that a

marked increase in the blood histamine may occur in serum anaphylaxis in man or in constitutional reactions following the injection of too large a dose of pollen extract, such determinations do not appear to have been made.

The first presumptive evidence for a release of histamine in allergy was reported by Lewis and Grant.¹²⁵ They observed that the wheals produced by stroking patients with sensitive skins contained a substance with some of the pharmacologic properties of histamine. It was not, however, until Barsoum and Gaggum³³ published their method for the extraction of histamine in the blood that any quantitative studies were attempted. There followed a few reports indicating that the blood histamine was increased in patients who had asthmatic attacks.¹²⁶⁻¹²⁸ Following the modification of the method by Code,³² he and MacDonald³⁴ noted that the histamine content of the blood of normal (non-allergic) individuals remained remarkably stable and these results were confirmed by Rose.⁴⁵ MacDonald and Haworth¹²⁹ then studied a group of asthmatics and could find no significant change in the blood histamine during attacks as compared to quiescent periods. Similar results were later reported by Rose¹³⁰ on a larger group of patients. In contrast, Randolph and Rackemann³⁶ noted that the blood histamine was increased in some of their asthmatic patients during attacks. Since that time we have made many determinations of the blood histamine in patients with asthma, both in and out of attacks, without observing any correlation between the histamine content of the blood and the appearance of symptoms.¹³¹ As often as not, the blood histamine level was decreased during attacks as compared to quiescent periods. Studies on the blood histamine in patients with hay fever have yielded similar equivocal results.^{130,131} More significant perhaps are the observations of Myrhrman and Tomenius¹³⁴ who were able to show a marked increase in the histamine content of the stools of asthmatics as compared to those of normal subjects.

The sputum of asthmatics is said to contain histamine¹³⁷ and it has recently been found in the nasal secretion of patients with the common cold and rhinitis.¹³²

Evidence of a more direct and convincing nature has been obtained in the studies on allergy and other conditions of the skin. Marked variations in the histamine content of the blood were observed in patients with urticaria, angio-edema and chronic eczema.¹³⁰ In the former two a decrease was noted with the onset of symptoms and wheal formation whereas in eczema the histamine content of the blood was often found to be increased. Wide fluctuation in the blood histamine, however, did not seem to be related to the remissions or exacerbations at the time. By assaying the histamine content of the skin directly on biopsy material, Pellerat¹⁷ has shown that a decrease occurs following burns or freezing by ethyl chloride. The increase of histamine in the blood of patients following burns has been previously noted.^{139,140} The skin histamine was also decreased in various skin lesions of an allergic or other nature while the blood histamine was increased. Katz¹⁴¹ has shown that histamine is liberated from the skin of allergic patients when wheals are produced by the intradermal injection of antigen. On the other hand, Abramson and his co-workers¹⁴² were unable to detect histamine in similar wheals by the sensitive method of reversed iontophoresis.

The relationship of histamine to dermatographia was indicated by Kalk¹³³ who showed that following the production of wheals in sensitive patients one could detect the release of free HCl in the stomach. Similar findings were reported by Horton, Brown and Roth¹³⁵ in patients with hypersensitivity to cold and, as a result, they attributed the systemic reactions observed to a general release of histamine into the circulation. The first direct estimation of blood histamine in physical allergy was made by Capps and Young¹³⁶ who showed an increase in the blood histamine of a patient with photosensitivity following exposure to ultraviolet light. In earlier studies,

Rose³⁵ was able to show a transitory increase of the peripheral blood histamine in five of ten patients with dermatographia following the production of whealing and in two of three patients with cold sensitivity following the application of cold. In a recent more detailed study of two patients with hypersensitivity to cold these observations have been confirmed and somewhat amplified.¹³⁸ It was found that these clinically indistinguishable patients differed basically in that in one the symptoms were due to histamine release whereas in the other some other metabolite must have been involved. These conclusions were based in one of these patients on a release of histamine into the plasma following exposure to cold, reproduction of symptoms by histamine injection and complete inhibition of symptoms by the administration of antihistamine compounds. In the other none of these findings could be substantiated although exposure to cold resulted in the production of intense symptoms. In this connection, Peters and Silverman¹⁴³ studied a case of heat allergy and concluded that acetylcholine was probably the substance which mediated the reaction although they did not exclude histamine. These findings may explain the discrepancy in the results obtained by treatment of such patients with antihistamine compounds as reported by others.¹⁴⁰

In an attempt to explain the divergent findings of a normal high or low blood histamine level in patients with allergic manifestations, Rose^{138,145} observed the effects of both the subcutaneous and intravenous injection on histamine on the blood histamine level. It was first observed that general changes in the peripheral circulation, associated with flushing of the face and neck, were common to all subjects whether allergic or not. Allergic manifestations, such as the production of transient asthma, urticaria, changes in the nasal mucous membrane or production of headaches, could be produced only in those patients who actively suffered from such complaints. Thus, râles and difficult breathing were

noted only in asthmatic subjects. Such observations have been reported many times previously, notably by Weiss, Robb and Ellis.¹⁴⁶ The most recent contribution to this field is the interesting set of papers by Curry. He has observed that whereas the administration of histamine to normal subjects produces little or no effect on the vital capacity, a marked reduction occurs in the pulmonary vital capacity of patients who suffer from asthma following this procedure.^{147,148} Antihistamine compounds administered one hour beforehand could completely inhibit this effect.¹⁴⁹ Rose¹⁴⁵ has further shown that in man the symptoms of histamine administration can be produced without an increase in the blood histamine. During the intravenous administration of this compound, the total blood histamine may actually decrease. Such findings are not surprising when compared to the results obtained in burn or traumatic shock in man,^{140,150} the changes which occur in rabbits⁷⁷ and horse and calf anaphylaxis.⁸⁴ In the acute stages of all these phenomena the blood histamine is lower than normal.

Reference must again be made to the state of histamine in the blood. Since the bulk of the blood histamine is contained within the white cell elements and since in this form it is inactive, an increase in this component of the blood histamine need not signify activity. Code and MacDonald³⁴ showed that the blood histamine can be markedly increased in patients with certain blood dyscrasias. In studies on the relation of the blood histamine to the cellular compounds of the blood in man values of 1,000 γ /100 cc., nearly 500 times more than normal, have been found in patients with myelogenous leukemia.¹³⁸ Such patients are neither in shock nor allergic. Yet if this amount of histamine were suddenly released, one can readily imagine the dire consequences when it is known that as little as 7 gamma of base injected intravenously can lower the blood pressure anywhere from 15 to 80 mm. of Hg.¹⁵¹

The demonstration by Katz and Cohen,¹¹⁵ that the addition of antigen to the *in vitro*

blood of patients suffering from hay fever or asthma causes a sudden release from the cells into the plasma, is of fundamental importance. This is the counterpart of *in vitro* anaphylaxis as originally shown by Katz¹⁴¹ on rabbit blood. The effect of the administration of antihistamine compounds on the symptoms of various forms of allergy will be found reviewed in another section. Their ability to inhibit to a large extent the symptoms of hay fever and urticaria^{153,154} is not as evident in the treatment of asthma.^{155,156} That this may be a question of dosage seems possible according to McGavack et al.⁵⁰ However, certain aspects of their activity are pertinent. It should be noted that they may inhibit other substances such as acetylcholine, as well as hyaluronidase, as recently demonstrated by Mayer.¹⁵⁷ The implications of this latter observation are obvious when the activity of hyaluronidase as a "spreading factor" is recalled. Thus, these compounds do not provide absolute proof that the substance inhibited is histamine. Even the itching of various skin lesions, which seems to be so effectively controlled in the majority of instances, can be attributed to their anesthetic quality which is three times as potent as procaine.¹⁵⁸

Of considerable interest is the work of Ahlmark¹⁵⁹ who has demonstrated a marked increase in the histaminase content of the plasma of women during pregnancy. He has shown that whereas little or no activity exists in the plasma of man or non-pregnant women there is a marked increase in pregnancy which reaches its peak by the seventh month. These results have recently been confirmed by Rose et al.¹⁶⁰ Although the significance of this marked increase in plasma histaminase is not understood, since there is no alteration of the blood histamine during pregnancy,¹⁶¹ it may have some bearing on the frequent observation that women suffering from any of the common allergic manifestations, such as asthma, hay fever or eczema, are often freed of their complaints when they become pregnant.¹⁶² Here again it must be remembered that plasma cholinesterase is increased as well¹⁶³

and in this connection Curry¹⁴⁸ has shown that the tracheobronchial tree of patients with asthma is even more susceptible to the effects of mecholyl chloride than to histamine.

Much attention has recently been drawn to the possible allergic nature of demyelinating diseases of the central nervous system.¹⁶⁴⁻¹⁶⁶ On this basis histamine has been advocated as a therapeutic agent in the treatment of disseminated sclerosis.¹⁶⁷ It should perhaps again be pointed out that while tissue damage of a permanent nature, with associated morphologic changes, may arise from antigen-antibody reaction, these changes do not result from the administration of histamine itself. That tissue lesions based on antibody-antigen reaction may occur in man is suggested by the recent work of Cavelti.¹⁵² However, the basic mechanism of such damage is still obscure and it must be reiterated that the release of histamine, if and when it occurs, is the result and not the cause of such damage.

In summary, it seems evident that two factors must be operative in patients with allergic disease with reference to histamine effects. These are: first, that the tissues must be hypersensitive to histamine and secondly, that there must be a shift of this substance from the intracellular or inactive form to the extracellular or free state. If this occurs in a local area of skin or mucous membrane, the amount of histamine released could hardly produce an increase in plasma histamine without causing systemic effects. When large amounts are liberated suddenly into the plasma, as in certain cases of hypersensitivity to cold, systemic effects become manifest. It should be noted, however, that such an increase is very transient in nature because of the rapid removal of histamine by body mechanisms. It seems probable that small amounts of histamine may be continually released in some cases of allergy, producing local symptoms, and rapidly removed from the blood by means of kidney or intestine as evidenced by the increased histamine content of urine and feces under these conditions. A marked increase in the

total blood histamine without alteration of the plasma histamine is completely compatible with absence of symptoms.

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The Antihistaminic Drugs^{*}

Pharmacology and Therapeutic Effects

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THE rapid developments in the field of antihistaminic drugs have resulted in enough confusion and misunderstanding to justify an attempt to summarize and evaluate the various phases of the subject. This paper consists of an evaluation of the essential experimental findings as well as clinical experiences with a number of antihistaminic drugs, some of which are already available to the general medical profession and one or two others which are still in the trial stage at the time of this writing. Although this presentation will cover the work of other authors as fully as possible, it will stress mainly my own clinical and experimental experience.

HISTORICAL BACKGROUND

The histamine theory for the mechanism of anaphylaxis proposed by Dale and Laidlaw¹ and the concept of histamine release in the allergic reaction suggested by Lewis and Grant² have been corroborated and amplified by many experiments. Even though there are evident reasons to justify the belief that some of the manifestations of allergy and anaphylaxis cannot be explained by histamine alone, there is almost unanimous agreement that histamine plays a prominent rôle in the phenomena of hypersensitiveness. This realization has led in recent years to a concerted effort to find substances antagonistic to histamine.

The amino acids, particularly histidine, cysteine and arginine, were among the first effective antihistaminic and antianaphylactic materials.³ However, the ratio of their toxicity to their efficiency was so great as to

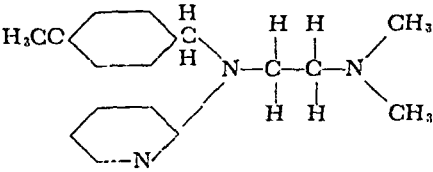
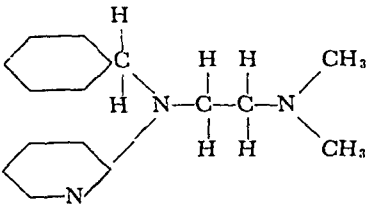
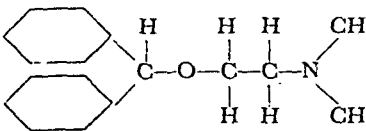
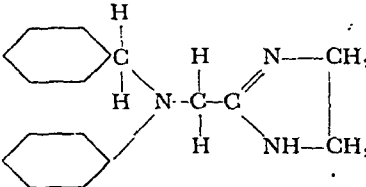
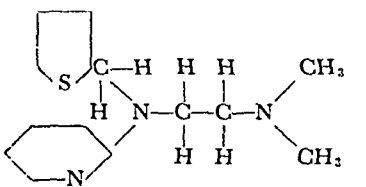
make their use impracticable. In 1933, Fourneau and Bovet⁴ reported that certain of their series of synthesized phenolic ethers had the ability to counteract the action of histamine *in vivo* and *in vitro*. This was the impetus for the production of a series of such compounds. Among the most promising of these were thymoxyethyldiethylamine (929F)⁵ and N-phenyl-N-ethyl-N'diethylethylenediamine (1571F).⁶ These compounds, however, were also too toxic in proportion to their antianaphylactic and antihistaminic activity.

The efficacy of the ethylenediamine radical in 1571F was recognized and there began a further series of syntheses and trials of chemicals containing this radical. These efforts finally resulted in the first drug sufficiently effective to be used clinically, N'phenyl-N'benzyl-N-dimethylethylenediamine, or antergan (2339RP).⁷ This drug was first used clinically in France and found to be effective in the symptomatic relief of many allergic manifestations. The ratio of therapeutic efficiency to toxicity in antergan was still not sufficiently favorable.

CHEMISTRY OF MODERN ANTIHISTAMINICS

Although I shall stress the experimental and clinical findings of the drugs at present on the American market (benadryl and pyribenzamine), I shall also briefly speak about others which are available outside of this country and of one or two others which shortly may be available here. The names and structural formulas of these drugs are as follows:

^{*} From the Department of Medicine, Division of Allergy, Northwestern University Medical School, Chicago, Ill.

Structural Formula	Chemical Name	Trade Name	Manufacturer
	N- <i>p</i> -methoxybenzyl-N-dimethyl-aminoethyl- α -aminopyridine	Neoantergan	Rhone-Poulenc Co. Paris, France
	N'pyridyl-N'benzyl-N-dimethylethylenediamine	Pyribenzamine	Ciba Pharmaceutical Products, Inc. Summit, New Jersey
	β -dimethylaminoethyl benzohydryl ether	Benadryl	Parke, Davis & Co. Detroit, Michigan
	2-(N-phenyl-N-benzyl aminoethyl)-imidazoline	Antistine	Ciba, Basle Basle, Switzerland
	N-(2-pyridyl)-N-(2-thenyl)-N', N'-dimethylethylenediamine	Thenylene (Abbott) Histadyl (Lilly)	Abbott Laboratories North Chicago, Ill. Eli Lilly & Co. Indianapolis, Ind.

EXPERIMENTAL AND PHARMACOLOGIC

The pharmacologic effects in animals and man are quite the same with each of these drugs although they may differ quantitatively in individual activities.⁸ The status of their comparative activities is, however, in confusion because of the tendency for experimenters to vary their experimental technics both qualitatively and quantitatively. I shall therefore refrain at this time from emphasizing quantitative differences between these drugs and shall limit my discussion chiefly to their major similarities.

Antihistamine Action. Any one of these drugs administered to animals such as guinea pigs, dogs and cats is capable of pre-

venting fatal shock from histamine when injected intravenously. One type of experiment consists of noting the number of lethal intravenous doses of histamine tolerated by guinea pigs after a fairly large dose of the protective drug is given intraperitoneally. In such an experiment, for example, we found that 3 mg. of the drug per Kg. of animal protected against five lethal doses of histamine with benadryl, thirty-seven with pyribenzamine and 125 with neoantergan. We soon learned, however, that such comparisons do not give an accurate conception of the efficacy of the drug. Such tremendous doses of histamine are far removed from the probable amounts released during anaphy-

laxis and the allergic reaction. The action of these drugs in preventing fatality from one lethal dose of histamine was regarded as more closely approximating physiologic conditions. On that basis we found⁹ that the difference between such drugs as benadryl and neoantergan was not nearly as striking.

Prevention of Bronchospasm from Aerosolized Histamine. The inhalation of aerosolized histamine by guinea pigs produces bronchospasm and dyspnea which progress to convulsions and death if exposure is continued. The prevention of these histamine effects by the prior administration of a protective drug has been utilized as a measure of antihistamine activity. Unfortunately, the technics of the various experimenters differ in many respects.¹⁰⁻¹⁴ The route, dose and time of administration of the protective drug, as well as the concentration of histamine, time of exposure and details of administration may vary radically. Even the end point differs materially. Many take death as the criterion, others convulsions and still others the first evidence of unquestioned dyspnea. For these reasons it is hardly ever possible to make fair comparisons of the efficiency of these actions of different drugs as reported by different experimenters.

Nevertheless, the experience of others as well as our own indicates that judged by such general methods both pyribenzamine and neoantergan are highly effective in preventing bronchospasm. We have performed similar experiments using dyspnea as an end point and administering the protective drug not only by the usual route but by inhalation. These experiments were carried out with a wide variety of antihistaminic drugs and the details will be published elsewhere. We shall confine ourselves here to the drugs under discussion. Pyribenzamine and neoantergan were of a high order of efficiency in the prevention of dyspnea due to aerosolized histamine. Benadryl, the thenyl compound and antistine showed definite protection but not as marked as was obtained with the other drugs.

Histamine Contraction of Intestinal Strip of Guinea Pig. If an antihistaminic drug is

added to the bath in which a piece of guinea pig ileum is suspended, the contraction normally produced by histamine will be prevented by the addition of the antihistaminic agent. All drugs of the type described are capable of producing this effect.^{11,14-17} We have utilized this method quantitatively in a comparative study of a large series of drugs. The findings with all of these drugs and a critique of the method will be given elsewhere. We may state here that of the drugs considered in this paper, pyribenzamine and neoantergan were the most effective, that is, the least concentration of the drug was required to inhibit contraction produced by a standard amount of histamine. The other drugs, however, also showed a high degree of this property. Contractions produced by other spasmogenic substances, i.e., barium chloride or acetylcholine, were prevented to an appreciable extent by benadryl; the other drugs had only slight inhibitory effect.

Antiwealing Properties. In most types of allergic manifestations localized edema as a result of capillary permeability changes is the most characteristic phenomenon. Since a histamine wheal can readily be produced in the skin of man, it was thought that observations on the inhibition of wheals produced by histamine and other whealing agents might throw light on the potency of the drugs and their possible mode of action. By applying solutions of these drugs to scratches of the skin either prior to or in combination with the application of histamine, we were able to show¹⁸ that these drugs inhibit whealing due to histamine. By varying the histamine concentration in a series of scratches while keeping the antihistamine concentration constant or by reversing the procedure, we were able to arrive at an approximation of the potency of this antiwealing effect. Elsewhere we shall discuss in detail the data obtained by comparative studies of this phenomenon with a large series of drugs. At present suffice it to say that the drugs discussed here were all active in this respect. In addition we found that the wheals produced by antigen-anti-

body reaction, codeine and similar substances, were also inhibited. Last and Loew,¹⁹ in studies with benadryl and neoantergan on capillary permeability in rabbit skin, found that these drugs prevented or diminished the action of injected histamine but did not inhibit other agents causing increased permeability. I would suggest that this discrepancy may be due to the fact that rabbit skin is not as suitable as human skin for such studies.

Other Properties of Histamine. These drugs will combat the depressor effect of histamine on the blood pressure of the cat or dog. Although such observations are not complete for all drugs, none of the drugs studied from this viewpoint showed any ability to inhibit the histamine function of stimulating gastric secretions.²⁰ As a matter of fact, Halpern has pointed out²¹ that when guinea pigs survive histamine shock from very large doses of histamine (300 MLD or more) by virtue of being subjected to large doses of the antihistaminic drugs, they are apt to develop acute perforating gastric ulcers in twenty-four to forty-eight hours. I have been able to corroborate this finding. The presumptive explanation is, of course, that this particular function of histamine, the stimulation of gastric secretion, is not inhibited by the antihistaminic drugs, thus allowing the excess histamine to produce gastric hypersecretion and an acute ulcer. It should be noted that McGavack and his associates²² claim that gastric secretion in man is depressed by benadryl. As time progresses we may find a number of functions of histamine which the so-called antihistaminic drugs are unable to combat.

Antianaphylaxis. The drugs under consideration have been found effective in the prevention of anaphylactic shock in guinea pigs and other laboratory animals.^{11,15,23,24,25} Our experience indicates that these drugs differ much less in this property than in their antihistaminic action. The antianaphylactic effect could also be demonstrated on the sensitized guinea pig ileum *in vitro*. In our preliminary work⁹ it was indicated that less drug was required to

inhibit an anaphylactic contraction than a histamine contraction of similar magnitude. Such a finding would tend to cast some doubt on the concept that histamine release is responsible for the anaphylactic contractions. However, more extensive experience indicates that the variations in the anaphylactic contractility of various segments of the ileum of the same animal are so great that any conclusions based on the activity of different strips may be questioned.

Other Pharmacologic Actions. The drugs under discussion here (and other antihistaminic drugs) have a local anesthetic action. It is suggested by some that it is this local anesthetic action which is responsible for the relief of pruritus and possibly for other histamine effects. That this explanation is doubtful is indicated by the relatively small doses required for antiallergic effects as compared with the local analgesic action. These drugs are similar in that in small doses (in man) they produce sedation while with fairly large doses excitation is produced in animals and also in man.

The toxicity of these drugs has been investigated in various species of animals. In general, one may say that there are no striking differences between the drugs in toxicity studies although there is considerable variation in their sedative action in man. It is established that the present series of drugs and most of the other new ones have much more favorable antihistaminic toxicity ratios than the amino acids or the early synthetic antihistamine compounds. Chronic toxicity studies in animals have thus far been practically negative.

CLINICAL

Considerable confusion exists with regard to the clinical action and function of the antihistaminic drugs. It should be clearly understood that they are solely palliative forms of medication. A dose of the drug may be effective for several hours, frequently only for two hours. Most observers agree that there is no tendency for cumulative effects or persistence of action after the drug has been discontinued, even after a pro-

longed period of administration. It is absolutely futile to have a patient take such a drug for weeks or days or even hours preceding an anticipated allergic episode such as seasonal hay fever. As a matter of fact, such abuse of this therapy may do harm because tolerance to the drug may result from long continued use.

The action of these drugs is limited. They do not correct all of the manifestations of histamine or allergic action nor do they relieve any particular symptom completely. For example, the stimulation of gastric secretion by histamine is not inhibited, asthma is very little affected and many types of allergic manifestations are not benefited. Even in allergic phenomena in which the drug works well, urticaria or allergic rhinitis for example, 100 per cent inhibition of the lesion or symptom is practically unknown. The histamine antagonists are most efficacious in the patient who is on allergic management when the drug is made to serve as an aid to allergic therapy rather than as a substitute for it. The need for avoidance of allergens cannot be replaced by drug therapy nor are the antihistaminic agents substitutes for the more complete and lasting tolerance possible by desensitization. Antispasmodics, vasoconstrictors and expectorants are still important remedial agents, sometimes as adjuncts to the histamine antagonists and at other times superior to them.

Hay Fever and Perennial Allergic Rhinitis. Last year I reported on a series of 254 seasonal hay fever patients of whom 82 per cent received benefit from pyribenzamine and on 130 patients with perennial vasomotor rhinitis of whom 64 per cent were helped.^{26,27} Our subsequent experience has been about the same. Others²⁸⁻³¹ have reported comparable results. Our experience with neoantergan^{26,32} in various types of allergic rhinitis was also satisfactory but not quite as good as with pyribenzamine. Bovet and his associates³³ report excellent results with neoantergan. Benadryl was also of help in these cases but the incidence and degree of relief were considerably less than

with the other two drugs. Some workers have claimed^{34,35,36} better results from benadryl than I have been able to obtain; one author³¹ has claimed results superior to those obtained with pyribenzamine. Our experience in the past year with antihistaminic compound histadyl, known as thenylene by another manufacturer, indicates that it also is a potent and useful drug in these conditions. Antistine is also of benefit in some cases^{37,38} but is much less consistent in its action than the other drugs.

These five drugs, as well as the other histamine antagonists not discussed here, display individualistic behavior toward patients. Perhaps it would be even more correct to say that each patient is individualistic in his behavior toward these drugs. One patient may benefit from drug A and not from B; the next patient may show an exactly opposite response. As a matter of fact, sometimes a drug of very low general efficacy may prove to be the best drug for a particular person.

As I have pointed out previously, the benefit derived in any one type of allergic ailment is limited. In allergic rhinitis the most marked result is in diminution of the hyperesthetic symptoms, itching and sneezing. The coryza is also pretty well controlled. The intranasal edema, however, responds less readily both in frequency and degree. One notices very often that the early symptoms of hay fever may be well controlled whereas the late congestive stage may not be benefited as much. Perhaps the greater resistance to antihistaminic therapy shown by perennial cases is due to the fact that nasal obstruction is apt to be a more marked feature in this type of allergic rhinitis.

In the more or less continuous phases of allergic rhinitis the drug should be used three or four times daily, usually in 50 mg. doses in the adult. When the symptoms are irregular, it is best to take the medication as needed and repeat in four to six hours if necessary. When the symptoms are confined to the morning hours, a dose of the drug on arising or after breakfast will suffice. In a good many patients, taking the

medication at bedtime may result not only in a better night but frequently in a better morning. The combination of ephedrine with the histamine antagonist may produce greater effects, particularly on nasal blocking. When sedation from the antihistaminic becomes objectionable, the addition of a cerebral stimulant such as amphetamine or desoxyephedrine may solve the difficulty. I have found, however, that in most instances I could solve this problem even better by substituting another type of antihistaminic drug. Since in some individuals these drugs produce excessive dryness of the throat, measures to combat the latter may be necessary.

In speaking of benefit from these drugs the statistics refer, of course, only to the number of persons helped and do not indicate the extent of benefit derived. The percentages are impressive but the degree of relief in many instances is far from satisfactory. The mild cases are helped more readily. By the same token, those whose hay fever has been partially improved by desensitization are more likely to obtain worth while effects from the antihistaminic drugs.

Asthma and Allergic Cough. Asthma does not respond well to these drugs^{27,33,36,37,38} although more favorable results are reported by some authors.^{22,39,40,41} In a small percentage they are of some benefit but the degree of relief does not approach that obtained with the usual antiasthmatic drugs (ephedrine, epinephrine, aminophylline and iodides). The irritative preasthmatic or allergic cough responds more readily than the dyspnea and in this regard the action of these drugs may be better than that of the old antiasthmatic remedies. Children show a greater tendency to benefit than adults. At times, the combination of an antihistaminic drug with ephedrine or aminophylline, or both, may prove to be effective. I have noted a general misunderstanding among many physicians concerning the efficacy of these drugs in asthma. Very frequently I see patients with asthma who have been previously dosed with benadryl or pyribenzamine for weeks or

months without relief whereas a day or two of medication with the old antiasthma remedies quickly produced the desired result. In those patients who have asthma with their hay fever the latter may be strikingly benefited while the asthma is not affected. Since such associated asthma is effectively prevented by pollen desensitization, this constitutes a valid reason for not depending on the antihistaminic drugs in hay fever.

It is not clear why asthma should be so refractory to the antihistaminic drugs. One possible reason is that we may be dealing with a chemical mechanism in asthma which differs from that in hay fever. Another possibility is that the bronchial tissues may release a much greater concentration of histamine so that the amount of drug tolerated orally is insufficient to combat it. For this reason I have experimented with aerosols of antihistaminic drugs, particularly pyribenzamine. Although the technical problems are not entirely solved, it would seem possible not infrequently to obtain prompt relief with such therapy.

Urticaria, Serum Sickness and Dermographism. Pyribenzamine and benadryl have been about equally effective in the symptomatic improvement of urticaria.^{26,29,42-45} In approximately 80 per cent of patients with urticaria and angioneurotic edema worth while relief of the discomfort of itching is obtained. The edema is also diminished in many cases but not as consistently or as completely as the itching. In the serum sickness type of reactions consisting of urticaria or angioneurotic edema, arthralgia, fever and other symptoms occurring several days after the administration of serum, penicillin or sulfonamides, these drugs are also effective. The joint symptoms in these patients are, however, more resistant to palliation than the tissue edema. The acute urticarial dermatoses appear to respond better to antihistamine medication than the chronic. In severe cases the drug is required every three or four hours and large doses, such as 100 to 150 mg., may be necessary. In such instances pyribenzamine has the advantage

because larger doses are usually better tolerated than benadryl. The thenyl compound and neoantergan^{32,33,46} have also been effective in these conditions. Good results have also been claimed for antistine^{37,38,47} but in our experience its effectiveness is not dependable. There is no evidence whatever to indicate that any of these drugs shorten the course of the urticaria or serum sickness.

One of the first clinical conditions in which the antihistaminic drugs were used was dermatographia.⁴⁸ The improvement in itching and welting prompted us to try these compounds as prophylactic medication prior to the performance of specific skin tests in allergy studies of those patients whose dermatographism prevented accurate interpretation of the tests. This was successful in the majority of such patients. One or two doses of the drug taken orally one hour and three or four hours prior to the performance of the tests eliminated most of the skin irritability while interfering very little with the specific skin response to the antigen. It is important, however, to keep in mind that such premedication might conceivably inhibit mild skin reactions sufficiently so that they become negative.

Atopic Dermatitis and Other Types of Dermatitis and Pruritus. The itching of atopic dermatitis (flexural eczema, infantile eczema, neurodermatitis) has been helped materially in most patients by the oral use of antihistaminic drugs.^{26,28,29,30,33,44,45,47} While usually only the itching is influenced, it happens not infrequently that discontinuance of the scratching may result in improvement of the skin condition. In many instances the drug is required only at night. When sedation is of advantage, benadryl may act more favorably than pyribenzamine. On the other hand, because of its greater sedative action, benadryl can rarely be used in ambulatory patients when large doses are required. Although there is individual variation in response to the different drugs, benadryl and pyribenzamine produce about the same incidence of relief. Neoantergan and the thenyl compound are also

effective. It should be clearly understood that a goodly number of patients fail to obtain any degree of relief from these drugs.

The itching of contact dermatitis was helped in some instances but not as frequently as in atopic dermatitis. In dermatophytosis, eczema of the hands and itching dermatoses of unidentified types relief was sufficiently frequent to justify a trial of these drugs. Pruritus ani and pruritus vulvae were benefited in most instances by pyribenzamine. In a few cases in which we tried benadryl, neoantergan and the thenyl compound similar relief was obtained. In other types of generalized pruritus there was occasional relief but in most of them, contrary to the experience of some other workers, no benefit was obtained.

Since we had shown¹⁸ that antihistaminic drugs applied locally inhibit the wheal and itching of histamine or the specific antigen, it was believed that topical application of such a drug as pyribenzamine might be useful in itching dermatoses. After considerable experimentation with solutions, emulsions and ointments of various concentrations we finally decided that a 2 per cent ointment of pyribenzamine hydrochloride in a water-washable ointment or a similar strength of pyribenzamine base in a petrolatum material was the most useful. Such ointments applied locally not only may augment the effects of the drug given orally but may even be effective at times when the latter fails. This topical therapy⁴⁹ has been most useful in atopic dermatitis, particularly when the lesions are not too acute. Such therapy should not be used when the skin is raw or weeping. The ointment has been very helpful in a number of instances of pruritus ani. In other types of dermatoses with itching benefit was also obtained but not so regularly.

Miscellaneous Conditions. The data on gastrointestinal allergy are meager. My own experience indicates that these drugs may help or prevent such manifestations but not in all instances by any means. McGavack and his associates²² report relief of two cases of spastic colon and nine of functional

dysmenorrhea by the use of benadryl. My experience with migraine has not been very encouraging although some clinical reports present favorable results. I have seen the pruritus and the edema of a patient with dermatomyositis materially helped by pyribenzamine. There has been some claim²² that cardiac asthma has been improved in some instances. Other conditions in which some degree of benefit has been claimed are insect bites and erythema multiforme. The itching and edema of a marked local reaction from the injection of a specific antigen during desensitization therapy can be benefited by a dose of one of the drugs. In the prevention of systemic reactions from desensitization therapy a 50 mg. dose of pyribenzamine or similar drug taken thirty to sixty minutes prior to the injection may prevent the reaction and allow increments in antigen doses not otherwise possible. In my experience, however, this action is only moderately quantitative, that is, it is not sufficiently great to prevent reactions from excessive dose increments.

ADMINISTRATION AND DOSAGE

The antihistaminic drugs are generally administered orally, in the form of tablet, capsule or liquid. The usual dose for adults is 50 mg. A few patients respond to smaller doses while some require 100 or even 150 mg. The large doses are not as well tolerated with benadryl as they are with pyribenzamine. Antistine requires larger doses than the other drugs. The dosage of benadryl or pyribenzamine in children under ten is 25 mg. but 50 mg. doses may be used if the smaller amounts are ineffective. For infants we usually give 10 to 20 mg. in the form of an elixir.

The frequency of administration depends on the allergic manifestation and its behavior in the individual patient. For example, if the itching of atopic dermatitis is troublesome only at night, a dose of the drug at bedtime is sufficient. If the allergic rhinitis manifests itself only for a couple of hours in the morning, medication on arising would be indicated. Frequently I have noted that

a dose of medicine at bedtime may prevent the severe sneezing spell in the morning. When the symptoms are more or less continuous, three or four daily doses and sometimes even more are required. At times, the addition of ephedrine, aminophylline or both may be of synergistic help particularly in asthma. If the antihistaminic drug produces marked sedation, it may be combined with the above drugs or with dexephedrine or benzedrine.

Benadryl can be given intramuscularly in doses of 10 mg. or more. Benadryl, pyribenzamine and antistine have been administered intravenously. Such modes of administration are seldom indicated and when considered advisable should be used cautiously.

I have already referred to other forms of administration: ointments, which may be of help in itching dermatoses and aerosols of pyribenzamine, which may be of aid in some instances in the relief of the allergic cough. Antistine has also been used in eye drops.

UNDESIRABLE ACTIONS AND TOXICITY

Side reactions from antihistaminic drugs are rather frequent. Sedation, differing mainly in degree, is one manifestation that is common to practically all of these and other related drugs not discussed here. Of the drugs discussed in this paper benadryl produces the most marked sedation, antistine the least while the other drugs are intermediate in this action. The sleepiness from benadryl may be so intense that the patient may be unable to be on his feet. Other undesirable actions noted with these drugs are dizziness, lassitude and dryness of the mouth and nose. Additional effects noted at times have been palpitation, headache, gastrointestinal irritation, dysuria, constipation and tightness in the chest.

More serious untoward reactions have also been noted particularly with benadryl. The hypnotic effect of benadryl may promote accidents.⁵⁰ Disorientation,⁵¹ marked excitation, epileptiform movements and irrational mind⁵² have been reported. Other toxic effects noted have been neuritic

pains⁵³ and reactions ending in circulatory collapse⁵⁴ and unconsciousness. A case of granulocytopenia probably due to pyribenzamine has been described.⁵⁵ Two cases of generalized eruptions following the use of pyribenzamine for atopic eczema have been reported.⁵⁶

It is apparent that many of the side actions may be highly undesirable. One or two of the newer drugs, not discussed in this presentation, may be found to be freer from such unpleasant actions. It is important to keep in mind, however, that the possible remote toxic effects from these drugs are still not fully ascertained and may perhaps constitute the greatest hazard. Prolonged observation of blood counts, liver function and other tests will be required to answer this question for every new drug.

SUMMARY

1. The chemical structure of several antihistaminic drugs—benadryl, pyribenzamine, neoantergan, antistine and thenylene—is described.

2. These drugs inhibit histamine shock, prevent bronchospasm following exposure to histamine aerosols in guinea pigs, inhibit the histamine contraction of the guinea pig intestinal strip, prevent the depressor effect of histamine on blood pressure, protect against anaphylactic shock and against contraction of the sensitized intestinal or uterine strip and inhibit the whealing action of histamine, specific antigens and other whealing substances. They also possess a local anesthetic action, act as cerebral excitants in large doses and some of them have an atropine-like action.

3. Clinically, these drugs offer symptomatic benefit to patients with allergic rhinitis, urticaria and angioneurotic edema, serum sickness, atopic dermatitis and many forms of pruritus. They are not very effective in asthma or migraine.

4. The unpleasant reactions are frequent with most of these drugs, benadryl displaying the highest incidence and the most marked effects. Sedation is the outstanding side action. Other unpleasant actions of the

drugs are dizziness, dryness of the mouth and nose, weakness, headache, insomnia and gastrointestinal disturbances.

5. More serious toxic actions have been noted. It is important that the possibility of remote toxic effects be constantly kept in mind.

6. It is emphasized that these drugs are not completely effective, that at best they are only palliative and that they do not relieve all phases of allergy. They are not substitutes for other antiallergic remedies such as epinephrine, ephedrine, aminophylline and iodides. While the antihistaminic drugs are valuable additions to our therapeutic armamentarium, they do not obviate the need for the more basic and lasting effects of specific allergic management by methods of avoidance and desensitization.

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Allergic Dermatitis*

A View of Its Immunologic and Biochemical Implications

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ALLERGIC dermatitis includes those inflammatory lesions believed to result from an altered state of tissue reactivity which renders the skin unusually sensitive to substances that ordinarily do not evoke grossly demonstrable reactions. The dermatitis may be acute. More often it is chronic with recurring exacerbations. The lesions are erythematous, vesicular or papular. In the more acute and active stage, when the epidermis is edematous, the lesion is frankly exudative or eczematous. Itching is the common symptom. It is often severe and leads to traumatization by scratching. Trauma is frequently a major factor in prolonging the dermatitis as may also be secondary pyogenic infection or mild irritation from numerous sources.

In the acute stage of dermatitis the skin has a mildly swollen appearance and histologically there is edema both of the vascular corium and the avascular epidermis. In the epidermis the presence of fluid gives a varying picture which depends upon the degree of edema. When minimal, there may be only vacuolization of the epithelial cells. When in excess, there is palpable vesiculation and in extreme cases bullous formation.

In the chronic stages of dermatitis the skin becomes dry and thickened, and the surface markings are exaggerated. This gives the skin a lichenified appearance. In both the acute and chronic phases there is disturbance of epithelial keratinization which gives rise to desquamation of the keratinized or partially keratinized cells. In extreme cases, as in arsenical dermatitis, there is often widespread exfoliation and the tissues are edematous and highly inflamed.

The terms used to describe the dermatitis are many. Eczema is perhaps the most common. When the lesion is chronic and the skin lichenified, it is at times called neurodermatitis. In addition there are terms which attempt to suggest the cause or some underlying mechanism. Among these are atopic dermatitis, contact dermatitis, or dermatitis venenata, and drug dermatitis, or dermatitis medicamentosa. These and still others would seem to fall within the scope of allergic dermatitis.

The allergic dermatoses have been placed in two categories depending upon the source of the excitant, and the route of contact, namely, intrinsic and extrinsic allergic dermatitis. In the intrinsic type the sensitizing agent enters the body chiefly through the gastrointestinal tract or by the vascular system as in the intravenous administration of therapeutic agents. In the extrinsic type contact is directly with the cutaneous surface.

This differentiation is of advantage only from a clinical point of view since it is doubtful whether the route of exposure carries any essential immunologic significance. It is generally assumed that the dermatitis in either case is related to an antigen-cellular antibody reaction. Although this explanation is based chiefly upon hypothetical grounds, the associated clinical circumstances and immunologic phenomena seem sufficient justification for the assumption. The theory will serve at least for the present even though it is probable that new knowledge will in time prove it inadequate as a definitive explanation.

It may be helpful to an understanding of

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the presently conceived relation of the integumentary system to the allergic state to consider briefly the historical developments which have brought these inflammatory lesions into the area of allergy. As early as 1895, Jadassohn showed that patients with eczematous dermatitis, attributed to extrinsic causes, reacted with a similar dermatitis when small amounts of the suspected exciting substance were applied directly to uninvolved areas. However, it was from a different direction that observations were to demonstrate more clearly the relationship. This was the introduction of horse serum to the treatment of diphtheria, with its attending serum sickness and associated cutaneous lesions, and the identification of this reaction with anaphylaxis. Even though the anaphylactic animal did not respond with cutaneous lesions characteristic of serum sickness in man, it was obvious that the urticarial wheal and its associated vascular phenomena were functions of sensitization to a foreign protein. The similarity of the cutaneous sensitivity demonstrated by Jadassohn in eczematous dermatitis to that accompanying serum sickness became apparent when it was shown that the skin of a person sensitized to horse serum reacted locally to the foreign protein and that skin sensitizing substances were demonstrable in the blood.

Postulates of Allergy. In testing for sensitivity two kinds of cutaneous response are observed in man: One is an immediate and transient reaction in the form of erythema and an urticarial wheal. This follows at the site of intradermal contact with the antigen. The other is a delayed response coming within twenty-four to forty-eight hours after direct contact of the unbroken skin with the antigen. This reaction is inflammatory and often vesicular.

In the immediate reaction the tissue changes are those of edema and hyperemia. They are temporary and reversible and are related to vasomotor disturbances and imperfections in permeability of the vascular membranes. Its clinical counterpart is urticaria and the functional erythemas, also

angioneurotic edema with its more profound disturbance in local fluid balance. In the respiratory tract there is a resemblance to the lesions of the mucous membranes in hay fever.

The delayed reaction affects both the corium and epidermis. The tissue changes, when well developed, are organic and hence not reversible except through the processes of repair. However, the restorative process can now be greatly accelerated in certain cases by special measures. At its maximum, necrosis of the skin may occur, as exemplified by the Arthus phenomenon. The delayed reaction has its clinical counterpart in exudative or eczematous dermatitis. It is analogous to the tuberculin type of reaction.

Although there is no specific histologic pattern which differentiates the allergic reaction, the frequent eosinophilic response may suggest the presence of allergy. Eosinophilia occurs with greater regularity and more prominently in the wheal-reacting form of allergy.

In the blood of the guinea pig and of man sensitized to horse serum are found specific antibodies. These are of three kinds, namely, precipitins, smooth muscle sensitizing substances and others capable of sensitizing the skin. It is around these functions of the sensitized organism, especially the skin-sensitizing antibody, that much of the argument as to the identification of a dermatitis as allergic has centered.

The differentiation of allergic disease in man depends upon the isolation of the offending allergen and the demonstration of its ability to excite the particular tissue or tissues to activity or upon amelioration of the reaction by removal from contact with the excited tissues. Secondly, it depends upon the demonstration of skin sensitivity to the specific antigen or of skin-sensitizing antibodies specific to the antigen, preferably both.

Although immunologic evidence of allergy may be demonstrated with some regularity in anaphylaxis and serum sickness, it is not so readily demonstrable in all the so-called allergic diseases of man. It is the

failure to satisfy the postulates of allergy and the inability, where these criteria are present, to relate them specifically to the clinical disease which has led to confusion. Often the results of such studies are equivocal and there is no way of establishing the relationship of the disease to the allergic state or of demonstrating what contribution the state of allergy may make to the pathogenesis of the lesion. It is with these uncertainties that we are faced in the study of allergic dermatitis.

Intrinsic and Extrinsic Sensitization. As we have already stated, allergic dermatitis may result from either intrinsic or extrinsic contact with the causative agent. While in some instances the form of lesion and the distribution of the eruption suggest the mode of contact, at other times this differentiation is quite impossible. When the contact is intrinsic one would expect to find the seat of reaction in the corium. There would be the usual signs of inflammation. The nature and form of the lesion would depend upon the grade of inflammation and the extent of edema and extravascular cellular infiltration. In the acute and milder grades of inflammation vascular dilatation and edema not differing much from the urticarial reaction would be present. No hard and fast line can be drawn at times between the urticarial and dermatitic response. One may occasionally observe an urticarial reaction, or something closely approaching it, preceding the inflammatory reaction. This is often true of arsenical dermatitis. The condition known as erythema multiforme is a classical example of a reaction that at one and the same time shows the signs of urticaria and dermatitis. It evolves with the suddenness of urticaria and lingers with the persistence of a dermatitis. Occasionally, it may show small hemorrhages into the skin or, perhaps, bullous edema. There may be lesions of the mucous and synovial membranes and involvement of the viscera. Osler once likened the condition to anaphylaxis. When the inflammatory process is more chronic, papulation of the skin

may be found and a state of lichenification may be present.

In the extrinsic form of dermatitis the epidermis is the primary seat of sensitization. As the epidermis is avascular and composed wholly of epithelial cells, inflammation necessarily takes a different form than in the highly vascular corium. The lesion consists of accumulated fluid and a vesicle or bulla is formed. Vesiculation is the mark of epidermal reaction and exudation that of vesicular rupture.

Actually, however, whether the injury comes from within or without, both the corium and the epidermis show signs of disease. It is only the preponderance of reaction in one or the other part of the skin which may suggest the primary seat of sensitization. The complex reaction comes from the rapid diffusion of the irritant from the corium into the epidermis, or vice versa.

Histamine. It has long been the impression that anaphylactic shock in the experimental animal and the allergic reaction in man may be related to a basic causative mechanism. It was early observed that the symptoms of anaphylactic shock were strikingly similar to those of histamine shock. Both Shultz and Dale were able to demonstrate that the isolated and perfused uterus of the sensitized guinea pig contracted forcefully upon contact with the sensitizing antigen in a manner identical with histamine. It was some twelve years later before the urticarial wheal was to be related to the same mechanism.

Lewis and Grant,¹ while studying the physiology of the blood vessels of the human skin, had their attention directed to the urticarial lesion which resulted from mechanical injury to the skin of certain susceptible persons said to be dermatographic. This urticarial response to a single firm stroke on the skin they believed was set in motion by a diffusible substance similar to histamine which was released in the skin by the stroke. Susceptible subjects differed from normal subjects only in their susceptibility to injury. All persons reacted in a similar manner when the grade of injury was suffi-

cient. Agents evoking the reaction had one property in common, namely, they produced damage to the tissues. By this action it was believed a substance is released which sets in motion a triple reaction consisting of a red line, a surrounding flush and a wheal. The first and last of the three components of this reaction are local in origin; the flush surrounding the wheal was shown to depend upon a nerve reflex. The triple response they considered a physiologic expression of a general mechanism of defense in the skin against injuries of all kinds. In the susceptible person it attracts attention only because of the relatively mild grade of injury required to liberate the diffusible substance.

Histamine is a normal metabolite which, according to Code,² is not the fundamental factor in anaphylaxis or in allergic reactions. It is liberated only as a consequence of damage done to the sensitized cells. It is the damage that is essential to the allergic or anaphylactic reaction; the liberation of histamine is purely incidental. Heparin is also liberated in some species and affects the coagulability of the blood.

In recent years it has been suggested that acetylcholine,³ a mediator of parasympathetic nerve impulses,⁴ is the chemical mediator of anaphylaxis or of the allergic reaction. There has been some speculation as to whether this effect might be due to an excess of acetylcholine or to inhibition of its catalysis through some defect of the choline esterases. Others were unable to demonstrate the presence of acetylcholine in excised tissues from allergic animals.⁵

Although it is possible that histamine may be released in allergic disease, there seems to be no direct evidence that such is the case. Fluctuations in the histamine content of the blood in patients with allergic diseases such as asthma, hay fever and dermatitis are greater than in normal man but are not necessarily correlated with the onset of symptoms. Rose⁶ could detect no variation in the histamine content of the blood in recurrent urticaria although others have noted an increase. In angioneurotic edema

the level of histamine in the blood showed a moderate to marked decrease while symptoms were at their height and returned to normal limits after their subsidence.

The action of the antihistamine substances, benadryl and pyribenzamine, on the manifestations of allergic disease in man have not clarified the position of histamine in the allergic reaction.⁷ Except in urticaria, these drugs have not controlled the reaction to a significant degree. Even in urticaria the results are variable and withdrawal of the drug is followed by the recurrence of lesions. There is little or no evidence that either benadryl or pyribenzamine affect allergic dermatitis except in allaying the itching. Nor would such an effect be expected in view of the assumed relation of histamine to the allergic reaction.

Allergy and Dermatitis. The basis for the assumption that allergy is a force in the causation of dermatitis and that the mechanism is related to an antigen-cellular antibody reaction rests upon two prime observations: The first is its frequent occurrence in persons with an immediate urticarial type of cutaneous reaction to antigens derived from certain foods and inhalants. Such persons frequently also have or later come to develop allergic diseases such as hay fever and asthma. Among those individuals there is apt to be a familial history of allergic disease. The second factor is a manifest sensitivity to foreign substances in small quantity, substances which ordinarily are not productive of dermatitis and which cause entirely different effects in the allergic state than they do in the non-allergic state.

Related to the first is the dermatosis which by some is called atopic dermatitis, a term of doubtful propriety which includes the eczematous eruptions of infancy and childhood as well as similar dermatoses incident to adult life. All these, in the minds of most, are eczema.

The second includes the drug eruptions in which the immunologic and familial evidence of allergy found in the so-called atopic group is generally absent. Evidence of specific sensitization can often be adduced

in the drug sensitivities. There may be a tangible history of first exposure and the subsequent effect of the drug is often immediately apparent even to the patient. The second also identifies an extrinsic dermatitis due to contact with certain plants and chemicals. As in the drug sensitivities of intrinsic origin, immunologic and historic evidence of the allergic constitution is usually lacking. Unlike the drug allergies, however, there is greater difficulty in identifying the causative agent. Poison ivy and primula dermatitis are perhaps the best known examples of extrinsic allergic dermatitis.

The immediate urticarial skin reaction cannot be demonstrated in the chemical sensitivities whether they proceed from intrinsic or extrinsic contact. It seems possible, however, that this failure may be due to the use of the wrong allergen in that the simple chemical rather than its protein conjugate is used in the testing. In such cases, when specific cutaneous sensitivity can be demonstrated, it is a delayed inflammatory type of reaction not an urticarial reaction. There is good reason to suspect that the state of sensitivity existing in either case does not suffice to explain fully what goes on to produce the dermatitis.

Intrinsic Allergic Dermatitis. We will discuss two varieties of intrinsic allergic dermatitis: one occurs in infancy and childhood, the other in persons who become sensitized to arsenical drugs. The first is commonly known as infantile eczema or atopic dermatitis, names which we would prefer to replace with the simple term, exudative dermatitis. This name is fairly descriptive anatomically and, since the cause of the dermatitis remains obscure, carries no etiologic connotation. In older persons a similar dermatosis goes by various names, including neurodermatitis. We have chosen arsenical dermatitis as an example of the second variety of intrinsic allergic dermatitis because of our familiarity with it and also because recently acquired knowledge concerning it opens to view a mechanism which may have a significant bearing on dermatitis

from other causes. Although the dermatitis of infancy differs in many respects, historically, clinically and immunologically, from arsenical dermatitis, a fundamental similarity in their genesis seems not improbable.

Exudative Dermatitis of Infancy. The skin of the infant, whatever the nature of the injury, tends to react with a more edematous lesion than does the skin of the adult. The lesion is apt to be vesicular or bullous. Causes as diverse as the bite of an insect or infection with pyogenic cocci or *Treponema pallidum* frequently cause vesiculation or bullous formation in the infant. The epidermis, the seat of all such lesions, seems especially vulnerable to injury and reacts acutely in the only way given it, that is to say, by the accumulation of fluid. In the adult a well developed edematous component is less often observed, especially in the conditions mentioned above. The inflammatory reaction is often greater in the vascular corium where it is marked by a preponderance of extravascular cellular activity and edema. Such differences are perhaps only quantitative; nevertheless they indicate less stability of the epidermal tissues in infancy than in adult life. At least, allergic dermatitis in infancy is usually exudative and the skin has a plethoric appearance. In the adult the dermatitis is inclined to be hyperplastic and dry. Between the two extremes lie many variations.

Certain epidemiologic aspects of eczematous dermatitis in infancy have been repeatedly emphasized as significant indications of the allergic nature of the dermatitis. It is stated that as many as 50 per cent of infants with dermatitis give a familial history of allergic disease among their antecedents. A like history is obtainable from children who have asthma and hay fever. We were not, however, able to find any record of the frequency with which infants, unaffected by dermatitis or other allergic diseases, have a similar familial history. The statement is made that they do not; nevertheless it seems desirable for the sake of accuracy that this point be established beyond doubt. One criticism of similar con-

clusions drawn from the study of allergic disease is that they are often based on percentages dealing with highly selected samples, sometimes inadequate in number to give the noted differences statistical significance; or if the differences are of that magnitude, the bias introduced by the method of sampling is such as to invalidate the conclusions.

It is also asserted that 50 per cent of children who manifest eczematous dermatitis already have asthma or hay fever or will develop these diseases before they reach the age of ten years. This would appear to be a highly significant correlation. However, one would want to ask about those infants with dermatitis who do not grow up to have asthma, and hence are not taken into account; for it is assumed that only those who develop asthma later in life consult a physician and thus get into the clinical sample. In other words, the conclusion is based on a sample of asthmatic children and not upon the entire population of once eczematous infants.

Regardless of any fallacy which may be involved, we will assume for the purpose of the argument that ample reason exists for including the dermatitic and asthmatic children in the same group, thus relating dermatitis to allergy. Besides there are other functions which would relate the eczematous reaction to the allergic state. These have provided abundant reason for differences in opinion as to the significance of allergy in the causation of dermatitis.

Infants affected with dermatitis frequently carry skin-sensitizing antibodies in their blood and, when tested with antigens prepared from foods or inhalants, develop immediate wheal reactions at the site of contact. Multiple sensitivities occur in half of those tested. Among 100 such infants whom Hill⁸ tested, local wheal reactions to egg albumin appeared in eighty-seven infants, twenty-six reacted to milk and seventeen to wheat. It was his belief that "sensitivity to the protein of cow's milk is probably the most important single cause of atopic dermatitis in infancy." Concerning

egg white, to which most of the infants reacted, he concluded that it could be of little importance as a causative factor in the dermatitis since most of the infants had never eaten eggs; and when it was removed from the diet of those who had eaten it, there was usually no effect on the dermatitis. So far as egg was concerned, it seemed necessary to differentiate the allergic state from allergic disease. But what of milk? By the same token was there any more reason to implicate it than the egg? Apparently not, for the same author went on to say, "I have seen nothing in the literature, including my own contributions, which leads me to believe that anyone really understands infantile eczema or that there is now any method of treatment, dietetic or otherwise, that is consistently and entirely satisfactory." It seems altogether probable that too much significance has been attached to the immediate wheal of the skin test in the eczematous child and, for that matter, in the eczematous adult.

It remains obscure why the infant who at birth shows no sensitivity to egg white later develops this sensitivity without having eaten eggs. The phenomenon seems to occur in those infants predisposed genetically to the allergic state and later to allergic disease. Those who do not possess this apparently heritable capacity do not develop skin-sensitizing antibodies, even when fed egg white in quantity, nor do they develop dermatitis, asthma or hay fever.

It has been demonstrated that 30 per cent of millers and bakers who are exposed to cereal dusts have wheal reactions to skin tests with cereal antigens but normally manifest no disease from this exposure.⁹ At the other extreme is the person who, receiving an injection of horse serum for the first time, dies in anaphylactic shock. And as yet no one, by artificial sensitization of man, has succeeded in producing any of the diseases attributed to allergy which spontaneously develop at different ages.

In eliminating the wheal-reacting type of allergy as of immediate significance in the production of allergic dermatitis, there are

the revealing observations of Hampton, Wing, Boker and Cooke¹⁰ who tested approximately sixty infants and children, all with typical eczematous dermatitis. This they did by passive transfer of skin sensitivity through the use of blood serum. Half of those tested gave positive wheal reactions to foods and inhalants. The others gave no reaction. The nature and course of the dermatitis were the same in both groups. The familial incidence of allergic disease was also equally divided. Asthma was present in ten patients.

In a second group of twenty-seven patients, who were hospitalized for dietetic study, fifteen had asthma, urticaria or hay fever in addition to dermatitis. When tested by passive transfer, the serum of seventeen children gave typical immediate wheals to one or several foods. In thirteen instances these tests were verified by a direct skin test. In an attempt to prove or disprove the causal relationship of the allergen giving a positive skin reaction to the dermatitis, it was found that the foods concerned could be eaten abundantly and continuously without any exudative skin reaction. In patients acutely sensitive to egg, peanut or honey, feeding of these foods caused urticaria to appear promptly but never dermatitis. The children could eat all other foods in quantity and indefinitely without developing any exacerbation of the dermatitis. It was thought that inhalant antigens such as pollens, danders and dusts could be excluded readily as causes of the dermatitis.

These observations afford the most critical test yet to be reported which would nullify the factor of specific sensitivity to foods and inhalants as the principal cause of allergic dermatitis in infancy and childhood. The presence of skin-sensitizing antibodies of the immediate wheal reaction type does not specify the dermatitis as being directly related to the allergen or allergens responsible for the positive results of the skin tests. Nonetheless, the frequent association of the allergic state with the dermatitis would indicate that enhanced tissue sensitivity contributes in some way to the readiness

with which cutaneous tissues respond to an injury not yet identifiable.

Thus far the central interest in the problem of allergic dermatitis has been directed toward the immunologic aspects of the disease and the technics of investigation have consequently been limited to those of the immunologist. But the results have been indifferent; a fresh point of view is badly needed. It is somewhat surprising, therefore, that until recently so little attention has been given to the observations of Hansen and his co-workers¹¹ who, in 1933, published the first of a continuing series of papers dealing with the essential fatty acids and the eczematous patient. It is not unlikely that from this or similar advances in the problem will come knowledge which in time may identify important metabolic faults as essential factors in the causation of eczematous dermatitis of this type.

Seborrheic Dermatitis. Seborrheic manifestations often precede an exudative dermatitis in the infant,⁸ especially in fat babies in the early months of life. The process may begin with intertriginous inflammation in the large folds of the skin or as greasy scaliness of the scalp, the so-called cradle cap. From thence the eruption may extend to the face, neck and to the trunk. The lesion is a dry scaliness with only faint signs of inflammation. There is no exudation. The scales may be so dry and profuse at times as to suggest psoriasis; more often they are yellowish and greasy. Unlike eczematous dermatitis, itching is not a symptom nor does the skin react to the tests for protein sensitivity. There is no evidence of an allergic state. After a few weeks or months, permanent recovery may ensue or the skin may become eczematous and exudative dermatitis may develop with demonstrable allergic sensitivity.

The sequence of seborrheic and exudative dermatitis occurs often enough to suggest a causal relationship. The fact, that in the one there is, as a rule, no evidence of allergic sensitivity and in the other such evidence is so often adduceable, leads one to suspect

that the development of cutaneous sensitivity may be a factor in the metamorphosis.*

Drug Dermatitis. Idiosyncrasy to certain drugs and chemicals is manifest in a variety of cutaneous disorders in man, usually after the first contact or at times after prolonged contact with a substance that had been well tolerated. Only small doses of the drug are required subsequently to evoke the cutaneous response often reproducible over a long period of time. The similarity to protein sensitization led von Pirquet to include the drug idiosyncrasies among the allergic diseases. Investigations were later carried out on the sensitization of animals to simple compounds of a non-protein nature known to cause hypersensitiveness in man. Arsphenamine was found to produce "symptoms like those seen in anaphylaxis" in guinea pigs which were sensitized with a mixture of the drug and homologous serum and then injected with the same mixture after a suitable period of incubation.¹² Others observed cutaneous reactions in guinea pigs sensitized to arsphenamine but found the reaction variable with the diet, namely, green fodder inhibited and dry fodder favored the sensitization.¹³ Cutaneous sensitivity through extrinsic contact was induced by *p*-phenylenediamine but with greater ease, perhaps because of its firm chemical union with proteins of the skin after oxidation.¹⁴ And more recently, anaphylactic shock has been produced with simple chemical compounds, for example, in animals sensitized to azoproteins and injected with azodyes having the same azo component.¹⁵ The reaction was specific and occurred with quantities of the dye as small as a fraction of a milligram.

Most authors thought the simplest explanation of the mechanism of hypersensitiveness to simple chemical compounds was

* In North China, exudative dermatitis of infancy is an infrequent disease among the mass of common people as is also seborrheic dermatitis. This fact may carry some significance in view of the dietary habits of these people¹¹ and the observed high unsaturation of their serum fatty acids.¹² Dietary fat is derived almost entirely from vegetable oils, the bulk of which consists of unsaturated fatty acids.

to relate them to the familiar processes of immunization, especially in view of the specificity of the reactions, and to assume a combination of the compounds with protein (as was probable in the case of *p*-phenylenediamine). Rabbits had also been sensitized to formaldehyde by immunizing them with formalinized protein.¹⁶ Then Landsteiner got the same effects by using arsphenamine alone.¹⁷

Perhaps the chief difficulty in explaining the phenomenon of hypersensitiveness to the chemical substances lay in the uncertainty of demonstrating circulating antibodies even in the pronounced cases of human drug sensitivity. How important an objection this may be remains a question. Nevertheless, it is not necessarily true that when no antibodies are demonstrable in the blood they may not be on the sensitized cells. However this may be, there are reports of the occasional demonstration of such antibodies in cases of human idiosyncrasy to iodoform, iodine, mercury and to other similar substances. Recently, sulfadiazine has been added to the simple chemical compounds shown to stimulate the formation of demonstrable antibodies in man and to react with these antibodies in the passively sensitized skin.¹⁸ From such evidence there would seem to be ample reason for including the drug eruptions among the allergic dermatoses.

The variety of anatomic lesions caused by drugs is limited only by the skin's capacity of reaction. No one form of lesion is identified with any one drug although certain drugs tend to produce lesions of similar character. Arsphenamine, for example, causes reactions which vary from a simple urticaria to exfoliative dermatitis, with the intermediate lesions of multiform erythema and purpura. Not infrequently all may be observed in the same person as they develop in sequence from urticaria to diffuse erythematous dermatitis with edema, exudation and, finally, exfoliation. At times the reaction is transient, as in urticaria; or again it may persist for weeks and even months as a severe inflammatory and ex-

foliative process. Other drugs such as the sulfonamides may cause bullous formations which merge into chronic exfoliative dermatitis; or again hemorrhage may be the only sign of sensitization in the form of purpura when the skin is involved or of diffuse bleeding in other organs such as the brain. Nodose erythema occurs at times with the bromides and nodose periarteritis with the sulfonamides.^{19,20}

In their action as antigens, drugs not only vary in the form of lesion produced and in the organ affected but also, like living pathogenic organisms, they vary in the ease and frequency with which they cause disease in different species and individuals.

While many of the cutaneous lesions occurring in drug sensitization are erythematous and urticarial in type and perhaps caused by the release of a histamine-like depressor substance, most are of the delayed reaction type in the form of a dermatitis which is indicative of a more profound and lasting derangement of cellular metabolism. The inflammatory lesions are not immediately reversible as are the urticarial lesions. During the period of acute urticarial response, adrenalin often effects prompt resolution of the lesion as in serum sickness and at times in the urticarias of drug sensitization. The antihistamine drugs, benadryl and pyribenzamine, act likewise but when the reaction has gone beyond the early stage of whealing and hyperemia, as in the multiform erythematous lesions and dermatitis of arsphenamine sensitivity, they are ineffective except as they may allay the itching. Inasmuch as the dermatitis in such cases continues to be progressive beyond the period of effectiveness of the antihistamine drugs, it is only reasonable to assume that factors other than histamine must be sought to explain the dermatitis. When once the process has become inflammatory, the urticarial phase of the reaction vanishes not again to appear. If histamine is a force in the production of the cutaneous lesion, it must act early and not after cellular degeneration has commenced. It seems not unlikely that once the junction of antigen

and antibody has taken place, presumably with the release of a histamine-like substance, the process is carried forward by other mechanisms quite distinct from the antigen-cellular antibody reaction.

Extrinsic Allergic Dermatitis. The extrinsic type of allergic dermatitis differs from the intrinsic variety primarily in the route of contact with the sensitizing agent. The site of sensitization is initially in the epidermis, the outermost layer of which is composed of a protein, keratin, together with an admixture of fats. Hence it is the epidermis which develops the preponderant reaction, with extreme grades of vesiculation like that seen in poison ivy dermatitis. Almost at once, however, hyperemia also appears. Although this phase of the reaction is often moderate as compared with that in the epidermis, it indicates the rapid diffusion of the excitant, or a derivative, into the denser and more vascular structures of the corium. Unlike some cases of intrinsic dermatitis due to chemical substances the initial urticarial phase of reaction is absent. From the first the lesion appears inflammatory.

In the drug eruptions as well as in eczematous dermatitis of infancy the initial reaction is in the corium but this is almost always followed either by mild edematous or vesicular changes of varying grades in the epidermis. The skin reacts as a whole. For this and other reasons, even though it is convenient to consider allergic dermatitis as either extrinsic or intrinsic, little is to be gained from holding to this convention longer than to establish the facts of contact. The reaction in either case is apparently actuated by the same or closely related mechanisms and these would appear to be closely related to that of anaphylaxis. This would seem to be true at least of the dermatoses following chemical sensitization. In the case of eczematous dermatitis of childhood and its counterpart in the adult, the parallelism is more obscure. Nonetheless, in thinking of the allergic dermatoses it seems reasonable and desirable to hold them as intimately related to a common factor, namely, a state of altered tissue reactivity

in which the threshold of tissue resistance is lowered.

Increased irritability is acquired by previous contact with the allergen. This is shown in the case of sensitivity to poison ivy by observations on the infant soon after birth²¹ and on the Eskimo²² who has always resided beyond the zone of exposure. In both, the absence of cutaneous sensitivity to contact with extractives of the poison ivy plant, *Rhus toxicodendron*, has been demonstrated. However, a few weeks later, 75 per cent of the infants who at birth were found non-reactive responded with a dermatitis at the area of second contact, showing that they had been sensitized by the first exposure. It is estimated that a similar incidence of reactivity exists in the adult population of the United States. In England primula or primrose dermatitis is prevalent. As in the case of poison ivy, after the application of the leaf of *Primula obconica* for several days to the skin of a normal person, without any sign of reaction, an acute dermatitis was found to appear on the second day after the leaf was again applied if an interval of several weeks had elapsed between the two applications.²³

The frequency of sensitivity to poison ivy in America corresponds to that for horse serum in those previously exposed by treatment. Other environmental substances which at times provoke dermatitis do not show this widespread distribution of sensitization in the population. Schwartz and Tulipan²⁴ state that in twelve industries, where continuous contact with known sensitizing chemicals exists, the annual incidence of allergic dermatitis is around 1 per cent. A similar incidence of sulfonamide sensitization is suspected. It is of interest, too, that about the same percentage of infants is estimated to develop eczematous dermatitis.

Sensitization with Simple Chemical Compounds. The mechanism by which simple chemical substances sensitize tissues has been the cause of much study. The fact that *p*-phenylenediamine (ursol), a sensitizing agent commonly employed in the dyeing of fur and hair, upon oxidation combines

readily and firmly with proteins, led to the assumption that the chemical is active antigenically because of a protein conjugate formed in the tissues. Strong evidence of this was found in a study of chloro- and nitro-substituted benzenes. One of these substances, 1,2,4-chlorodinitrobenzene, is a frequent cause of allergic dermatitis in factories where it is handled. As there are theoretically more than 90 chloro- and nitro-substitution products of benzene, it was possible to study the correlation between sensitizing capacity and any chemical characteristic. It turned out that those products which do not sensitize the skin were resistant to treatment with an organic base (aniline) and with one exception to treatment with sodium methylate and ethylate. Those that were potent sensitizers contained loosely bound Cl or NO₂ and formed substitution compounds with aniline by interacting with the amino group. From these observations Landsteiner²⁵ concluded that the sensitizing chemical, 1,2,4-chlorodinitrobenzene, and compounds having similar chemical activity depended upon conjugation in the body, probably with proteins. These findings were corroborated on human beings.²⁶

This led to a study of similar compounds such as acyl and benzoyl chlorides and acid anhydrides. These, too, were found to sensitize animals, presumably through their union with proteins in the body. Most informative, however, was the relationship between reactions of the skin and anaphylaxis caused by acyl chlorides. Guinea pigs were sensitized with *p*-chlorobenzoyl chloride injected intracutaneously. After a suitable interval, the skin was found to react with a dermatitis after direct application of the substance, and when a compound of *p*-chlorobenzoyl chloride and guinea pig serum was injected intravenously the animals developed typical anaphylactic shock. From these observations it was inferred that the two types of allergic manifestation are closely related.^{27, 27a}

In the case of extrinsic dermatitis in man, sensitivity can be demonstrated only by sur-

face contact with the allergen. The reaction is delayed and in the form of a dermatitis. Skin-sensitizing antibodies of the immediate wheal reaction cannot be demonstrated in the blood nor can sensitivity of the delayed reaction type be produced by passive transfer to normal subjects.

The production of cutaneous sensitivity of the delayed reaction type is far more easily achieved experimentally by direct application of the antigen than by other routes which as a rule are not effective. When sensitization has been established, however, introduction of the allergen through the gastrointestinal tract or through the blood may evoke a dermatitis at the previously sensitized area. This is observed in human cases of mercurial and sulfonamide sensitivity. To our knowledge it does not occur naturally in sensitization to poison ivy in which it would appear that direct contact with the excitant is required to produce a dermatitis. It is also worthy of note that in the extrinsic form of allergy in man the skin plays the most prominent if not the only rôle in the allergic process. Desensitization of the skin has not been achieved. Eosinophilia does not develop as it does in the intrinsic form nor is there any reason to believe that histamine takes any part in the reaction.

The question has arisen in view of these facts whether or not the skin can be sensitized directly without the participation of free antibodies as by the contiguous distribution of the allergen through the skin from epithelial cell to epithelial cell. If circulating antibodies are not present, it is necessary to account for the phenomenon of generalized sensitivity of the skin which exists in many cases. This question seems to have been definitely settled by Landsteiner and Chase²⁸ who showed that the allergen is transported by way of the lymph vessels lying on the surface of the muscular layer in the skin of the guinea pig. When these vessels were interrupted, sensitization beyond an isolated area of original contact did not take place.

BIOCHEMISTRY OF VESICULATION

Vesiculation or lesser grades of epidermal edema are characteristic of allergic dermatitis. For this reason it seems not unlikely that the biochemical lesion of artificially induced vesiculation may be closely related to that of allergic dermatitis. Some vesicants are known to be antigenic. Others are related chemically to the trivalent arsenical arsphenamine which sensitizes man and causes dermatitis. The same chemical substance, which prevents vesication upon contact with lewisite and other arsenical vesicants or restores the damaged skin, also has a curative action in allergic arsphenamine dermatitis. These facts strongly suggest a common biochemical mechanism. Even should this prove to be an unwarranted assumption, the facts as they exist are so intriguing that a discussion of their possible implication is desirable.

The vesicant action of arsenicals and other similar substances is conditioned by their ability to penetrate the keratin layer of the skin and thus reach the site of blister formation in the epidermis and also of vascular reaction in the small blood vessels of the deeper layers. In some instances, as with arsenious oxide, only prolonged and intimate contact with the skin may produce erythema and vesication. The arsenical vesicant, lewisite, being lipid-soluble, rapidly penetrates the epidermis where it is hydrolyzed immediately to the corresponding toxic oxides.²⁹

There is now an impressive body of evidence that the toxic effects of arsenicals are primarily related to the fact that they combine with —SH groups in the tissues and thus inhibit enzyme systems essential to cellular metabolism. When arsenic combines with tissue proteins, reactive —SH groups disappear^{30,31} and the closer the union the more serious the effect on the cell. A series of enzyme proteins containing free —SH groups are reversibly inactivated *in vitro* by arsenicals with the disappearance of titratable —SH groups.³² This implies that

the toxic action of arsenicals is referable to similar sulfhydryl enzymes in living cells.

When lewisite ($\text{ClCH}=\text{CH}\cdot\text{AsCl}_2$) reacts with keratin, 75 per cent of the bound arsenic is in combination with two thiol groups.²⁹ This suggested the formation of a relatively stable ring structure. It seemed possible, therefore, that the high toxicity of trivalent arsenicals might be due to their combination with essential —SH groups in certain tissue proteins to form stable arsenical rings. If this assumption were correct, dithiols might combine to form relatively stable ring compounds with lewisite or other trivalent arsenicals and so compete effectively with dithiols of tissue proteins to protect the enzyme systems.^{33,34}

It was discovered that all vesicants, which comprise a heterogeneous group of most diverse chemical characteristics, inhibited carbohydrate metabolism of the skin, indicating that carbohydrates could no longer be utilized. There is strong circumstantial evidence that many vesicants act at the stage of initial phosphorylation of glucose by poisoning hexokinase, an essential intracellular —SH enzyme and one which catalyses glycolysis at this point. The pyruvate oxidase system is especially sensitive to poisoning by the arsenicals. In the case of mustard gas, however, it seemed improbable that the poisoning was due to an attack on —SH groups. There was a striking correlation between the vesicating property of any vesicant and its power to alter hexokinase. Reasons were also given for believing that phosphate-transferring enzymes, phosphokinases, belonging to the same group as hexokinase, are inhibited.^{29,35}

Some compounds not previously known to be vesicants were found to inhibit the enzyme. Further examination of these showed the apparent lack of vesicancy to be due to rapid evaporation; when held tightly to the skin, vesiculation developed. Non-vesicants always failed to inhibit glycolysis, except that one or two alkyl halides, which produced only edema, gave partial inhibition. The presence of glucose protected the enzyme to some extent and with high con-

centrations a few vesicants failed to inhibit the enzyme.

The original thesis that the dithiols might act to protect glycolysis was brilliantly established.^{33,34} It was proved that the cyclic thioarsenite formed by the interaction of simple dithiols and trivalent arsenicals was more stable than those formed by the interaction of tissue proteins and dithiols. Because of this, the simple dithiols could compete successfully with tissue proteins for such arsenicals as lewisite or phenyldichlorarsine.

This has been amply demonstrated in arsenical dermatitis in man.^{36,37} Arsenic bound in the tissues is released as shown by an increased excretion in the urine coincident with the rapid and complete regression of dermatitis.³⁸ Severe dermatitis from contact with diphenylamine chlorarsine, present as long as eighteen to fifty days, resolved rapidly and completely within two to eight days after the application of the dithiol, 2,3-dimercaptopropanol (BAL or dimercaprol), in ointment to the involved or even to the non-inflamed skin. Arsphenamine dermatitis likewise responded.

In this connection it is worth recalling recent observations regarding the irritating toxicants of poison ivy and related plants of the Anacardiaceae.³⁹ These are phenols or catechols characterized by a long unsaturated side chain attached to the ring. The reduction of the dermatitis-producing properties of these compounds both *in vitro* and on the human skin may be achieved by the action of mushroom tyrosinase.

The susceptibility of the skin to irritants varies with the species and in the same species among individuals. The skin of the rabbit is resistant to lewisite and reacts only with edema and hyperemia while that of man reacts violently. In both, however, inhibition of glycolysis is demonstrable; the difference is only quantitative.

There is a similar variation among chemical compounds in the power of vesicancy and, here again as in the living organism, variability differs only in the degree of damage to the tissues which they produce.

ALLERGY AND THE BIOCHEMICAL LESION

It is not so much the protective action of the dithiol, dimercaprol (BAL), which interests us as it is the power to restore integrity to the skin in a dermatitis induced by sensitivity to a known chemical compound and the ability to identify the dermatitis with a specific biochemical lesion developing during the allergic state.

Identification of the biochemical lesion is not, however, sufficient to relate the dermatitis directly to the state of sensitivity or to show why it is that the presence of cellular sensitivity predisposes to the biochemical lesion once sensitization has taken place. Perhaps, however, further consideration of arsphenamine sensitization and dermatitis may serve to clarify certain aspects of the relationship.

In arsenical dermatitis a common bond seems to exist between the immunologic and biochemical functions of the allergen. This may or may not be true of other allergens. Instead of the same substance acting both to sensitize the cells and then to poison an enzymatic system, it seems possible that each of these functions might be served by separate entities; one might sensitize, the other might inhibit certain metabolic functions of the cell. The action of the second need not be dynamic as in the case of arsenic; it could be passive as in the deficiency of an essential metabolite. Whatever the variation in detail, the result would be the same.

In any case the cohesiveness of cells and the barrier between the inside of the cell and the outside, the readiness with which the antigen reaches the cell and the ease with which the cell membrane admits molecules of varying dimensions and arrangements must necessarily be critical factors in determining the sensitization and destruction of the cell. It has been suggested that the cell membrane may be a lipo-protein structure,⁴⁰ the protein component with active patches rich in —SH groups adsorbed on an underlying lipoid envelope. If such were the case, the permeability of the membrane might

be affected by protein molecules denatured by a hapten with an affinity for sulfhydryl groups. With disturbance in the intercellular fluid matrix and increased permeability of the cellular membrane, changes in water balance would occur and the cell would be exposed to enzyme-inhibiting substances.

The case of arsphenamine dermatitis has several significant features. The immunologic properties of arsphenamine have already been discussed. Even though arsphenamine is immunologically active, it is not a vesicant under ordinary circumstances. Nevertheless, it may behave like a vesicant when applied directly to sensitized skin. This is demonstrated in the occasional patient recovered from an arsenical dermatitis. When a dilute solution of arsphenamine is applied to the intact and non-inflamed skin for a period of twenty-four hours or longer, a mild vesicular dermatitis has been observed to appear at the area of contact. This is the positive patch test. When small doses of the drug are given intravenously under such circumstances, dermatitis does not develop. Nevertheless, the allergic response may be measured by a sudden and transitory rise in eosinophiles in the blood. When doses of therapeutic size are given, a relapse of the dermatitis usually ensues. These facts carry a significant meaning for those cases of dermatitis growing out of sensitization to simple chemical compounds of the heavy metals. They may not, however, fully cover the dermatoses resulting from chemical substances of a different order.

Some of the powerful pupil constrictors, the miotics, such as the alkyl fluorophosphonates and eserine, are enzyme inhibitors.³⁵ These damage the choline esterases. This fact is of interest because of the probable function of acetylcholine and other vasodilators, such as histamine, in the production of the urticarial phenomena to which Lewis called attention in his study of factitial urticaria. To this we have previously referred. It also offers room for speculation on the neurogenic factor thought to be involved in the urticarias and angioneurotic edema and perhaps in certain cases of

dermatitis in which there may be disturbance in autonomic activity.

Although at present it is not clear how the eczematous dermatitis of childhood and its equivalent in the adult fit into this conception of allergic dermatitis, certain aspects of the eczematous reaction do seem to conform to this line of reasoning. First, the cutaneous reaction is vesicular even though not to the grade seen in poison ivy dermatitis or in some of the intrinsic chemical dermatides. It occurs in persons who are surely allergic, as judged by the presence of skin sensitizing antibodies in the blood, even though the specific sensitivities cannot be related directly to the dermatitis. In persons of eczematous constitution there is evidence of disturbed lipid metabolism as shown by alterations in the fatty acids of the blood. In dogs fed a fat-free diet, changes in the skin occur which in some respects are analogous to eczematous dermatitis or as nearly so as could be expected in a species naturally not responding with a vesicular reaction to any form of irritation. The lesion does, however, resemble quite closely seborrheic dermatitis. These changes can be prevented or the integrity of the damaged skin resorted by the feeding of lard which contains an abundance of unsaturated fatty acids. It seems not unlikely in time it may be found that the eczematous reaction in infancy depends on a deficiency in lipid metabolism superimposed on, or otherwise related to, the allergic state, and like the dermatitis of simple chemical sensitization to be dependent upon interruption of glycolysis or on some inability of sensitized cells to utilize the energy thus provided.

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Drug Allergy*

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THE consideration of allergies due to drugs separate from those due to other agents is, in a sense, an artificial distinction but is warranted by certain practical and theoretical aspects. While most of the common allergic diseases are easily recognized as such and their handling may be relegated to practitioners particularly interested in them, manifestations of drug allergy are commonly encountered in all kinds of medical and surgical practice and must be recognized by specialists in other fields.

Many of the symptoms of drug sensitivity such as fever, leukocytosis, arthralgia, lymphadenopathy, erythema nodosum and scarlatiniform and morbilliform rashes are familiar as manifestations of infectious disease, not of sensitization to naturally encountered extrinsic agents, and their allergic nature might well be questioned if they were not also characteristic of serum sickness which is known to be a protein sensitization. The practical importance of this similarity to infectious processes is attested by reports of fatalities which have resulted when drug fever due to sulfonamides has been confused with a recurrence of infection and the offending drug continued.¹⁻³

From the theoretical standpoint, there is reason to hope that further knowledge of drug allergy may contribute not only a broader concept of the manifestations of sensitization phenomena but also a better understanding of the rôle of allergy in the pathogenesis of many of the infectious diseases.

In this discussion, all agents introduced into the body for therapeutic or prophylactic purposes are considered drugs, the reaction to protein drugs such as hetero-

logous antisera forming a convenient link between the familiar protein sensitization and many of the allergies to non-protein crystalloid drugs. Different drugs vary widely in their capacity to produce sensitization, the allergenic activity having no relation to pharmacologic effects. Certain potent drugs such as epinephrine, caffeine and cascara sagrada are not known to cause sensitization while most of the familiar drugs produce such phenomena in occasional persons. A few drugs such as nirvanol and heterologous sera, in adequate doses, sensitize more than 90 per cent of patients.

The term "allergy" in this connection is less susceptible of precise definition. The word was originally introduced by von Pirquet to denote an altered reaction of an individual to repeated contact with an external agent; the presently accepted use of the term is limited to such reactions in which an antigen-antibody mechanism can be demonstrated or reasonably assumed to be present. Most of the naturally encountered allergens are substances not toxic to normal persons and when an individual shows an unusual reaction to one of them its allergic nature is usually manifest. In the case of idiosyncrasies to drugs, most of which in excessive doses are injurious to all individuals, the distinction between allergic and pharmacologic or toxic reactions is often difficult.

There are two criteria upon which the diagnosis of drug allergy may be made with certainty: First, the demonstration of antibodies which is usually possible in reactions to drugs of protein nature but rarely in cases of sensitization to crystalloid substances and second, the occurrence of symptoms typical of allergic disease such

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as asthma, rhinitis, urticaria or contact dermatitis which are entirely distinct from the pharmacologic actions of the drug. A considerable number of other drug reactions, in which an antibody mechanism has not been demonstrated, may be classed as presumably allergic because of the similarity of their symptoms to serum sickness or other known sensitizations particularly by the appearance of symptoms five to fourteen days after the first exposure to the drug which is the time characteristic of antibody formation. On this basis, the drug fever due to sulfanilamide was recognized by Hageman and Blake⁴ as a sensitization phenomenon although no antibody was demonstrable.

In recent years, Rich^{5,6} and other pathologists have considered certain histologic changes occurring in experimental protein sensitization as characteristic of the allergic reaction and the diagnosis of drug allergy has been made on pathologic grounds in the absence of immunologic evidence. The specificity of these lesions, which will be discussed later in greater detail, has been questioned by Klemperer⁷ and they are at present best considered as suggestive rather than diagnostic of allergy.

On the other hand, there are certain drug reactions in which a mechanism entirely unrelated to antigen and antibody is apparent and which can be readily excluded from the classification of drug allergy. Examples are hypersusceptibility to the normal pharmacologic or side actions of the drug and the mechanical results of crystallization of drugs such as sulfadiazine in the kidney tubules.

Between the groups of drug reactions which may be classified as allergic or non-allergic with reasonable certainty, are several important types of idiosyncrasy such as hepatitis, agranulocytosis and thrombocytopenia due to drugs in which the present knowledge of pathogenesis does not permit a definite distinction between sensitization and toxicity. These symptoms are not observed in the common allergic

diseases or known protein sensitizations* and an antibody mechanism is not demonstrable. However, these reactions resemble sensitizations in that certain individuals, after prolonged or repeated exposures to ordinary doses of drugs that at first cause no symptoms, suddenly develop an idiosyncrasy and the occurrence of such a reaction predisposes to recurrence on subsequent exposure to the same drug.⁸⁻¹¹ Loewy¹² classified these reactions as "allergotoxic" rather than "allergic" on the ground that certain idiosyncrasies were characteristic of each drug in contrast to the classical concept that sensitization phenomena are the same regardless of the causative agent. This distinction has lost most of its validity with the recognition that not only drugs but all allergens are limited in the sensitization phenomena they produce by the route of contact, solubility, distribution in the body and probably tissue affinity. Because of their clinical importance, these idiosyncrasies will be discussed further in order to elaborate on the evidence bearing on their classification as sensitization phenomena rather than as examples of proven drug allergy.

SYMPTOMS OF DRUG ALLERGY

Asthma and Rhinitis. Numerous drugs, proteins, vegetable gums and crystalloids may act as excitants of asthma and rhinitis on exposure by ingestion, parenteral injection or inhalation (usually occupational). In contrast to most other forms of drug allergy, these manifestations usually occur in persons predisposed by an hereditary tendency to allergy. The attacks precipitated by drugs may be interspersed with those due to other agents and indistinguishable from them. Among the protein drugs causing these symptoms are papain (caroid)¹³ and pancreatin. Persons with an

* Although acute thrombocytopenia is a feature of anaphylaxis in monkeys, and certain cases of Henoch's purpura have been shown to be due to food allergy, the reports of thrombocytopenia in man attributed to food allergy are not conclusive.

hereditary allergic tendency have been known to develop asthma on occupational exposure to tuberculin with an immediate urticarial reaction to intracutaneous test rather than the usual type of tuberculin sensitivity.¹⁴ The vegetable gums such as acacia, karaya and tragacanth produce the same type of symptoms. As commercially available and as used for skin tests, these gums contain nitrogen and there is no conclusive evidence whether the allergic reaction is to protein impurities or to the carbohydrate itself.¹⁵ One aspect of practical importance is the widespread pharmaceutical use of these gums as excipients, or cohesive agents, in the manufacture of pills. Brown and Crepea¹⁶ reported the case of a patient in whom the occurrence of asthma and urticaria following the use of pyribenzamine tablets was due to tragacanth used as an excipient and not to the pyribenzamine. Most pills contain some sort of gum, the presence of which is not noted on the label, and the possibility must be considered that reactions following their use may be due to allergy to the gum rather than to the pharmacologically active ingredient. Sensitivity to the gums is readily demonstrable by scratch or intracutaneous tests.

Among the crystalloid drugs producing asthma and rhinitis, aspirin is the most frequent offender but attacks due to quinine, sulfonamides,¹⁷ arsphenamine,¹⁸ penicillin¹⁹ and sulfonechloramides²⁰ have been reported. Asthma due to soluble and readily diffusible drugs is more immediate and severe than that due to protein antigens and fatal attacks have resulted from doses of 5 to 10 gr. of aspirin.^{21,22} It is a familiar clinical observation, as yet unexplained, that aspirin sensitivity is more often associated with the infective type of asthma than that due to foods or inhalants. As will be discussed in considering the immunologic aspects, skin tests with drugs such as aspirin are of no diagnostic value and are exceedingly dangerous.

Urticaria and Angio-edema. Urticaria and angio-edema are commonly caused by

drugs (proteins, gums or crystalloids) and in any case of unexplained urticaria all medications the patient is taking must be considered possible factors. Even thiamine, an essential constituent of the body, when injected parenterally in abnormal amounts, may cause a sensitization manifested by urticarial reactions and an immediate positive response to intracutaneous tests.²³⁻²⁵

Serum Sickness and Allied Reactions. The symptoms of serum sickness, fever, skin rashes (usually urticarial but often maculopapular or scarlatiniform), edema, lymphadenopathy, arthralgia (sometimes with effusions into the joints) and peripheral neuritis have been reviewed by Longcope,²⁶ Ratner²⁷ and others and need be mentioned only because of the frequency of similar manifestations in sensitizations to crystalloid drugs. The incubation period of five to fourteen days after the initial dose is characteristic as is the accelerated or immediate response to subsequent injections in the individual already sensitized.

Reactions indistinguishable from serum sickness, and with the same incubation period, are one of the most common manifestations of sensitization to penicillin of both the amorphous and crystalline forms. Many other drug reactions show one or more of the typical symptoms of serum sickness appearing after the same incubation period.

Anaphylactic Reactions. When heterologous serum is injected into a person already sensitized by a previous injection or with a spontaneous sensitization to this animal protein, the immediate, severe and often fatal reaction characterized by dyspnea, circulatory collapse, urticaria and angioedema resembles experimental anaphylaxis rather than ordinary serum sickness. Similar reactions in varying degrees of severity may occur after repeated parenteral injections of other biologic preparations containing foreign protein or proteose such as insulin,²⁸⁻³⁰ liver extract,³¹ toxoids³² and virus and rickettsial vaccines prepared from egg yolk.³³ In the case of persons naturally sensitive to egg yolk, severe reactions may

follow the first injection.* With the doses ordinarily employed, sensitization to these biologicals is much less frequently induced than with foreign sera and the serum sickness type of reaction does not follow the first injection into non-allergic persons.

Anaphylactic reactions (occasionally fatal) may also follow the intravenous injection of crystalloid drugs such as arsphenamine, quinine and thiamine.^{24,25} The response to oral administration of drugs is usually slower but a few of the acute, severe reactions to the sulfonamides may be considered in this category.^{34,35†}

Drug Fever. One of the most common but most frequently misinterpreted symptoms of drug allergy is fever. Nirvanol, a drug formerly used for the treatment of Sydenham's chorea, produced drug fever in 80 to 90 per cent of the patients who received adequate doses. Similar febrile reactions have been reported to all the common sulfonamide drugs the incidence varying from 2 to 16 per cent with the various drugs. The onset of fever is abrupt, most often on the seventh to tenth day, the incubation period corresponding to that of serum sickness and the usual time of antibody formation. Temperatures of 104 to 106°F. are not unusual, the fever is often but not always accompanied by a skin rash, usually maculopapular. The leukocyte count may remain normal or rise as high as 30,000 with a predominance of neutrophils, the eosinophils are only occasionally increased. When the drug is discontinued, the fever usually subsides in forty-eight to seventy-two hours; but subsequent doses after recovery cause an immediate recurrence. Short courses (two to five days) of the sulfonamides may produce sensitization but the drug may be completely eliminated before symptoms develop, so the allergy is

* Stull has reported an exceptional case in which injection of equine encephalitis vaccine, made from egg yolk, into a normal person produced a clinical sensitization to egg manifested by gastrointestinal symptoms after eating eggs.

† The mechanism of the severe and sometimes fatal collapse reactions following use of local anesthetics such as pontocaine and procaine has not been clearly established.

first manifested by an immediate reaction to subsequent use of the drug.³⁶ Among other types of drugs causing drug fever are iodides, thiouracil,³⁷ atabrine,³⁸ penicillin³⁹ and streptomycin.⁴⁰ The physiologic mechanism of drug fever is not known nor is its relation to the histologic changes attributed to drug allergy clear. While practically all patients with drug fever recover completely if the causative drug is stopped promptly, it is significant that fever and skin rashes have been outstanding symptoms in many of the cases in which necropsy has revealed extensive vascular and focal lesions.

Drug Rashes. Cutaneous eruptions are the most common manifestations of drug allergy and show many morphologic variations some of which, such as the acniform eruptions due to iodides and bromides, are typical of certain groups of drugs while others are produced by many different agents. The rashes due to the sulfonamides are fairly typical of the common varieties. When the sulfonamides are given by mouth, the incidence of skin rashes is 2 to 5 per cent. The first manifestation is usually a diffuse morbilliform rash appearing, with or without drug fever, on the seventh to fourteenth day of the initial course. If the drug is stopped promptly, the rash usually fades in a few days. If the drug is continued, the rash may progress either to purpura^{41,42} or to an intense confluent erythema going on to exfoliation.^{43,44} At this stage, the rash fades more slowly after elimination of the drug. The sulfonamides also act as photosensitizers and any of these rashes are made worse by exposure to sunlight.⁴⁴⁻⁴⁶ Once the skin has been sensitized by the occurrence of a maculopapular rash, subsequent doses of the same drug may produce an intense scarlatiniform rash within twenty-four hours.^{41,42,47} The topical application of sulfonamides may also give rise to contact dermatitis, usually a localized vesicular eruption. The controlled studies of Sulzberger and co-workers⁴⁸ showed that local applications of sulfonamides over a period of two weeks produced sensitization in 19 per cent of 253 cases, the incidence

being highest if the more soluble compounds, such as sodium sulfadiazine, were applied and also if the application was directed to inflamed or injured skin. Despite the differences in appearance of the eruptions resulting from internal and topical use, the fundamental skin sensitization is apparently similar and once established the reaction may be elicited by either form of contact. Thus, patients who have been sensitized by oral use often show positive patch tests³⁴ and develop dermatitis promptly on topical application of the drug while those who have recovered from contact dermatitis are apt to have local or general recurrences after oral administration. Although the contact dermatitis usually appears to be a local phenomenon without general reactions, patients with severe cases may develop fever up to 103°F.⁴⁹ and patients sensitized by surface contact may react to oral administration of the drug with chills, fever and marked eosinophilia, suggesting constitutional as well as skin sensitization.^{48,50,51}

Skin rashes essentially similar to those caused by sulfonamides are produced by numerous other drugs including quinine, mercury compounds, atabrine,³⁸ arsphenamine, thiouracil,⁵² penicillin and streptomycin.⁴⁰ In the case of drugs used both topically and internally, the same relationship between the dermatitis resulting from internal use and contact dermatitis is observed.

Contact dermatitis may also be produced by many other drugs used locally such as sulfur, formalin and procaine and other local anesthetics. It does not differ clinically from contact dermatitis due to non-medical agents many of which are non-protein in nature.

Space does not permit discussion of all the specialized forms of drug eruptions which have been reviewed by Sulzberger,⁵³ but two types warrant brief mention. Erythema nodosum is an eruption of characteristic clinical appearance and histologic features of histiocytic proliferation and perivascular infiltration not unlike some of

the visceral lesions attributed to sulfonamide sensitization. Lesions with the same clinical and pathologic appearance appear as manifestations of rheumatic fever, tuberculosis and reactions to drugs such as iodides, bromides, sulfonamides,⁵⁴ thiouracil⁵⁵ and penicillin.⁵⁶ When due to drug allergy, they usually appear after relatively long (three or more weeks) exposure to the causative drug, disappear in a few days when it is eliminated but recur promptly on subsequent administration. These lesions are believed to represent sensitization phenomena common to drugs and infections but which have not been known to be caused by other extrinsic allergens.

The fixed drug eruption is of interest as a striking example of localized tissue sensitivity to a systemically absorbed allergen. This type of reaction, caused by such drugs as phenolphthalein, antipyrine, amidopyrine, arsphenamine, alurate⁵⁷ and the sulfonamides,^{58,59} is characterized by the presence of sharply localized areas of skin or mucosa with an itching erythematous eruption which develops on ingestion of the causative drug. Between exposures the sensitive areas may appear normal or somewhat pigmented. The affected areas of the skin may or may not show positive reactions to patch tests with the exciting agent, the remainder of the skin invariably giving negative reactions. Several experimenters have exchanged skin grafts between the areas involved by fixed eruptions and other areas on the same patient but the results have not been uniform. Naegeli, de Guervain and Stalder⁶⁰ reported that a Thiersch graft from an area sensitive to antipyrine remained sensitive in its new site while Wise and Sulzberger⁶¹ and also Loveman⁵⁷ found that full-thickness grafts from areas sensitive to phenolphthalein and alurate, respectively, lost their sensitivities in new sites and that normal skin grafted into the affected area became sensitive. From the conflicting results it is not clear whether the sensitivity is inherent in the skin itself or in deeper structures such as the nerves and blood vessels supplying the area.

Hepatitis. Liver damage, which is possibly a sensitization phenomenon, occurs after the use of such drugs as arsphenamine, sulfonamides,^{62,63} cinchophen and atabrine.³⁸ All of these drugs are causative agents of drug fever and dermatitis and frequently the hepatitis is associated with a rash,^{11,38,62,64,65} usually exfoliative, which suggests the possibility that both are manifestations of a general sensitization. Hepatitis due to drugs usually appears after exposure over a period of one or more weeks⁶⁵ as long as or longer than the characteristic period of antibody formation. The relatively longer incubation periods may be explicable in that tissue changes in the liver are relatively advanced before clinical symptoms are apparent; the occasional appearance of jaundice several weeks after the last dose is difficult to correlate with known antigen-antibody reactions if it is actually due to the drug. When a second course of the same drug is given, hepatitis is more frequent and may appear within one to three days suggesting that sensitization has been acquired.^{11,65,66} The occurrence of one attack definitely predisposes to recurrence if the same drug is used again. The incidence and severity of hepatitis bears no relation to the dosage of the drug and the course is uncertain, some cases progressing to liver atrophy even if the causative drug is discontinued promptly.

Agranulocytosis. Leukopenia and agranulocytosis have been attributed to such drugs as amidopyrine, sulfonamides, arsphenamine, thiouracil and gold salts and, as previously noted, show certain features of a sensitization phenomenon. All of these drugs are frequent causes of typical drug allergies. Leukopenia occasionally occurs in patients who have previously manifested sensitization by the occurrence of a drug rash. Agranulocytosis may occur during the second week of continuous administration of amidopyrine⁸ while that due to sulfonamides occurs most often between the seventeenth and twenty-fifth days and that those due to thiouracil between the fourth and eighth weeks.³⁷ Prolonged administration of any of these drugs often causes a mild

decrease in the leukocyte count, which may or may not progress to dangerous levels, but in some cases agranulocytosis may occur suddenly. With the use of penicillin to control infection, a majority of patients with agranulocytosis recover within a few days after the causative drug is discontinued. After recovery trial doses of the suspected drug may cause a marked drop of the leukocyte count within a few hours, indicating destruction or elimination of circulating white cells as well as bone marrow damage.^{8,67,68} Other patients, in whom agranulocytosis or severe leukopenia have been attributed to sulfonamides⁶⁸ or thiouracil,⁶⁹ have subsequently been able to tolerate the same drug without reaction.

Thrombocytopenia. Thrombocytopenic purpura due to drugs has many of the features as agranulocytosis and both conditions may occur together as a result of bone marrow depression.^{70,71} In addition to the drugs causing agranulocytosis, sedormid¹² has been a frequent cause of thrombocytopenia. Usually purpura appears suddenly after use of the causative drug for a long period without symptoms but once sensitization is established single doses cause recurrence within twelve hours with the platelets dropping to 20,000.

SPECIFICITY OF DRUG ALLERGIES

The results of observations on the specificity of drug allergies are so variable that no generalizations are possible. This is best illustrated by sulfonamide sensitizations which have been most completely studied. Some patients sensitive to one sulfonamide drug have failed to react to any other members of the group.^{36,72,73} Other patients have reacted similarly to sulfadiazine, sulfathiazole and sulfapyridine but not to sulfanilamide.^{35,74} Still others have shown sensitivity to all drugs of the group.^{49,75} In some instances the sensitization was apparently to the para-aminophenyl radical and reactions were also obtained with sulfanilic acid, para-aminobenzoic acid and procaine.^{48,76,77} Park⁷⁷ reported that 60 per cent of sulfonamide skin sensitizations were

strictly specific for one drug while Sulzberger⁴⁸ found only 10 per cent who failed to show cross reactions. Dowling, Hirsch and Lepper⁷⁸ found that 69 per cent of sulfonamide sensitization reactions recurred if the same drug was used again but only 17 per cent if another drug of the group was substituted.

In sensitizations to other types of drugs, instances of both strict specificity and group reactions have been reported. Cooke⁷⁹ found that three aspirin-sensitive patients did not react to salicylic acid, benzoic acid, antipyrine, sodium acetate or methyl salicylate. Horsfall's⁸⁰ patient, exquisitely sensitive to formaldehyde, did not react to other aldehydes, formic acid or methyl alcohol. Loveman⁵⁷ reported a patient sensitive to alurate (allyl isopropyl barbituric acid) who did not react to barbituric acid or any of its other derivatives or to sedormid (allyl isopropylacetyl carbamide). On the other hand, Goodman⁸¹ described a case of a patient with procaine allergy who reacted to all the local anesthetics of the procaine group but not to those of the cocaine, quinoline or pyridine groups. Dawson and Gerbade⁸² reported a patient sensitive to quinine who reacted to seven related levorotatory compounds but not to quinidine, the dextroisomer of quinine, or to any of the corresponding dextrorotatory compounds. Patients sensitive to arsphenamine usually react to all the related compounds containing trivalent arsenic but not to tryparsamide in which arsenic is pentavalent. However, there are several reports of arsphenamine sensitization in which the reactions to trial doses of tryparsamide have been the same as those to compounds of trivalent arsenic.⁸³⁻⁸⁵ In a given case of drug allergy only cautious trial will reveal whether other related drugs are tolerated.

DURATION OF DRUG SENSITIZATION

Although few data have been published, it appears that the more severe drug allergies usually persist over a period of years. Cases of aspirin sensitization have been known to last for many years and there are reports of

patients allergic to sulfonamide still reacting promptly after one and one half to two years.⁸⁶ Robinson⁸⁷ reported a patient with arsphenamine dermatitis who remained sensitive after seventeen years. The most striking exceptions to this long duration are the allergic reactions to penicillin which are also exceptional in the frequency with which they subside while the causative drug is continued.^{88,89} Patients showing allergic symptoms from penicillin often tolerate a subsequent course after a few weeks or months without reaction.^{90,91} At first, these reactions were attributed to impurities which might be present in certain batches of the drug but the same response occurs when relatively pure crystalline penicillin is used. Hopkins and Lawrence⁹² demonstrated by skin tests and intramuscular injections that 30 per cent of penicillin-sensitive patients ceased to react within two to twelve weeks.

IMMUNOLOGIC FEATURES OF DRUG ALLERGY

The immunologic mechanism of serum sickness has been described by Longcope, MacKenzie, Rackemann and others and was reviewed by Longcope.²⁶ When a large amount of heterologous serum is injected into a non-sensitive person, the foreign protein remains demonstrable in the blood for many days; in exceptional cases in whom serum sickness does not develop as long as sixty-three days. Normally, however, serum acts as an antigen and after five to fourteen days, with the appearance of symptoms of serum sickness, a specific antibody demonstrable by precipitin, passive anaphylaxis and Prausnitz-Küstner technics appears in the circulation. During the course of serum sickness there is a gradual rise of antibody titre and a concomitant decrease of circulating antigen, the symptoms subsiding with the disappearance of antigen. After recovery the antibody remains present for months or years, the patient being in a state of anaphylactic sensitization during which time further injections of the same foreign serum produce an immediate violent reaction. This sensi-

tization, induced in normal persons, differs only in details from the spontaneous sensitivity of certain persons predisposed by a hereditary allergic factor in which the *first* dose of foreign serum causes a severe immediate reaction. Both forms of sensitization are readily demonstrable by intracutaneous, scratch or conjunctival tests with the specific antigen.

The anaphylactic type of sensitization produced by parenteral injection of other protein-containing biologic agents is immunologically similar except that, because of the smaller doses and more rapid elimination of the foreign protein, serum sickness does not follow the initial injection into a non-sensitive person. After sensitization is established circulating antibodies are present, although often demonstrable only by the Prausnitz-Küstner method of passive transfer, and reactions to scratch or intracutaneous tests are positive.^{28,33}

In delayed urticarial reactions to penicillin, clinically identical with serum sickness, a corresponding immunologic mechanism is not demonstrable. Some authors have reported the presence of positive intracutaneous tests^{56,89,93} and skin sensitizing antibodies⁹³ in such cases but other reports^{91,94-97} and extensive studies at The Roosevelt Hospital Allergy Clinic have shown that neither the skin test nor passive transfer is a reliable index of penicillin sensitivity. Small urticarial reactions to skin tests with penicillin may occur in non-sensitive persons and the tests are often completely negative during or shortly after an urticarial reaction. Skin sensitizing antibodies were demonstrable in the serum of less than 10 per cent of clinically sensitive patients and then in such low titres as to be of questionable significance. Also, if the reaction to penicillin occurs more than twenty-four hours after the last dose, the presence of the antigen cannot be demonstrated in the circulating blood as it may in serum sickness. However, it may be assumed that amounts of penicillin adequate for antigenic activity remain in the body during the reaction.

When the typical allergic diseases such as asthma, rhinitis, urticaria and angio-edema are produced by protein drugs or gums, their immunologic features are those characteristic of similar cases due to foods or inhalants. Scratch or intracutaneous tests with the causative agent give immediate wheal reactions and the characteristic skin sensitizing antibody, demonstrable by the Prausnitz-Küstner method of passive transfer but not by the precipitin technic, is present. However, when the same symptoms are produced by crystalloid drugs similar skin reactions and circulating antibodies are only rarely demonstrable. Immediate wheal reactions to skin tests and skin-sensitizing antibodies have been reported to quinine,^{82,98} thiamine,^{23,24} the sulfonechloramides²⁰ and sulfonamides³⁵ but in the vast majority of patients sensitive to crystalloid drugs such tests give negative results and no antibodies are demonstrable. Attempts at such skin tests are not only futile as diagnostic procedures but exceedingly dangerous since severe constitutional symptoms may result even in the absence of local reaction.^{99*}

The generally negative results of intracutaneous tests with crystalloid drugs and the failure to demonstrate circulating antibodies apply not only to the allergies manifested by asthma, rhinitis or urticaria but to all types of sensitization by crystalloid drugs. The classical methods of demonstrating antibodies have been developed from studies of protein antigens and are not entirely applicable to allergens of low molecular weight such as crystalloid drugs. The studies of Landsteiner¹⁰⁰ and others, showing that simple chemical compounds when combined with protein might act as haptenes and determine the specificity of antibody reactions, have helped to correlate sensitizations to crystalloid drugs with the familiar protein sensitizations. A number of drugs commonly causing sensitization such as formalin,¹⁰¹ sulfonamides¹⁰² and penicillin¹⁰³ have been

* Many drugs such as morphine, codeine, histamine and acetylcholine produce urticaria in normal skin and so are not suitable for intracutaneous tests.

shown to combine with body proteins and so might act as haptenes. However, the experimental sensitization produced by injecting artificial conjugates of drugs and protein into animals is of the anaphylactic type usually produced by protein antigens and does not resemble the reactions produced by the uncombined drugs in human beings.^{101,104} Guinea pigs sensitized by conjugates of sulfonamides with protein react to contact with the conjugate but not to the uncombined drug so the mechanism of the clinical drug reactions is not adequately explained. The use of artificial conjugates of drug and protein in the study of human drug allergy has been limited but so far has not contributed materially to the diagnosis or understanding of the phenomena.^{42,105}

A more simple method, adapting the hapten concept to the clinical diagnosis of drug allergy, was suggested by Leftwich.¹⁰⁶ He used sera of patients receiving adequate doses of the sulfonamide drugs (which presumably contained sulfonamide bound to protein) as antigens for intracutaneous tests of sensitivity to corresponding drugs. As a control, he injected serum obtained from the same patients when not receiving the drug. A difference of 4 mm. in the diameters of the test and control wheals was considered diagnostic and results consistent with the clinical evidence of sensitivity were obtained in twenty-eight of thirty patients. Confirmation of these results has not been published. Fink, Burton and Wheeler¹⁰⁷ obtained negative results with the same method in nineteen children and negative results in single cases of sensitivity in adults have been reported.^{54,108} Attempts to reproduce the phenomenon in patients known to be sensitive to sulfadiazine, at The Roosevelt Hospital Allergy Clinic, have failed. Intracutaneous injection of normal human serum, even of the patient's own serum, invariably produced a definite wheal and the size of the wheal produced by a serum containing sulfadiazine (blood level 9.6 mg./100 cc.) never differed significantly from that produced by the control serum. This test cannot be considered a reliable criterion for

the decision to give or withhold a valuable drug.

Until the demonstration by Landsteiner and Chase^{109,110} that the antibodies mediating the reactions of contact dermatitis and tuberculin sensitivity are present in the cells but not in the serum of sensitized animals, the study of allergic antibodies had been entirely confined to the circulating antibodies which are characteristic of protein sensitization. In addition to contact dermatitis, which is a common type of sensitization to non-protein compounds, there is reason to believe that many other drug allergies, for example fixed drug eruptions, are manifestations of tissue sensitivity. The methods employed by Landsteiner and Chase are not easily adaptable to clinical use but it is possible that the further development and utilization of technics for the study of cellular antibodies may demonstrate the immunologic mechanism of many drug allergies in which circulating antibodies are not present. Urbach¹¹¹ has suggested that blister fluid contains cellular antibodies not present in the serum.

Further light on the mechanism of contact dermatitis is given by the experiment of Haxthausen¹¹² who exchanged skin grafts between human identical twins, one twin of each pair being sensitized to dinitrochlorobenzene and the other not sensitized. The sensitive skin transferred to the normal individual lost its sensitivity while the normal skin acquired the reaction of the sensitive host. It was apparent that the skin cells transferred in the graft were not the important repository of antibody.

For purposes of diagnosis, the lesion of contact dermatitis may usually be reproduced by a patch test with the causative agent in a concentration which does not irritate normal skin. Occasional failures may result from the application of an agent producing dermatitis on delicate skin (such as that of the eyelids) to the tough skin of the extremities or back. As has been noted, dermatitis medicamentosa resulting from internal use of drugs has much in common with contact dermatitis and in many such

cases patch tests with the causative agent give positive reactions. These reactions, which may be elicited by such drugs as aspirin, sulfonamides, arsphenamine and penicillin, are frequently helpful in diagnosis but must be considered suggestive rather than diagnostic. A positive reaction obviously depends on the diffusibility of the drug through normal skin but, on the other hand, application of the drugs in relatively strong solutions may expose the cells to much higher concentrations than could result from internal use. Robinson⁸⁷ and others have found that the results of patch tests with neoarsphenamine, while often positive in patients who had had arsphenamine dermatitis, were not a reliable basis on which to prescribe treatment.

HISTOPATHOLOGY OF DRUG ALLERGIES

Largely as a result of the studies of Rich,⁵ the histologic changes occurring in drug reactions, particularly those due to the sulfonamides, have recently attracted considerable attention from pathologists. Longcope in 1913 to 1915,¹¹³⁻¹¹⁶ described inflammatory lesions in the kidneys, heart and liver of experimental animals receiving repeated injections of foreign protein. Further studies of experimental sensitization by Klinge,¹¹⁷ Vaubel,¹¹⁸ Knepper and Waaler,¹¹⁹ Masugi and Sato¹²⁰ and Rich and Gregory¹²¹ have demonstrated widespread foci of parenchymatous and collagen degeneration with monocytic infiltration and arterial lesions resembling those of periarteritis nodosa and rheumatic fever.

Similar lesions have been reported in patients dying during or after sulfonamide therapy, and occasionally with other types of drugs, without receiving any foreign protein injections. Many of these patients showed clinical evidence of drug allergy, such as drug fever or dermatitis, shortly before death. Rich⁵ has particularly stressed the presence of arterial lesions characterized by hyaline and fibrinoid degeneration of the media with perivascular infiltration of mononuclear and polymorphonuclear cells, including eosinophiles, which he considers

"typical, fresh lesions of periarteritis nodosa." Similar lesions have been described by other writers,^{3,66,122,123} some of whom hesitated to apply the term periarteritis nodosa. These lesions have been described in cases of patients with serum sickness¹²⁴ and sensitizations to iodine,¹²⁵ thiourea¹²⁶ and thiouracil⁵⁵ and so are considered a general manifestation of the sensitization reaction rather than typical of the sulfonamides. In addition to these vascular lesions, patients with sulfonamide reactions have shown focal necroses of the myocardium, liver, bone marrow, spleen, lymph nodes, lung, adrenal cortex and other organs, accompanied by focal or diffuse monocytic infiltration which may amount to granuloma formation or extensive interstitial myocarditis.^{66,122,123} The kidneys have also shown degenerative and interstitial changes similar to those present in other organs and apparently unrelated to the effects of crystalluria or hemoglobinuria.

The similarity of these changes to the lesions of certain infectious diseases such as typhoid fever, tularemia, scarlet fever, diphtheria and miliary tuberculosis has necessitated careful consideration of the possibility that they might have resulted from infection rather than from the drugs used. Patients suffering from the diseases mentioned have been excluded from the studies cited. In a number of instances, fatal reactions have followed the prophylactic administration of sulfonamides to previously healthy persons with injuries not apparently infected or after operative procedures at which evidence of infection was not noted. In one of Rich's¹²⁷ cases, biopsy specimens from the scrotum, obtained five months and again one week before a sulfathiazole reaction, showed no evidence of arteritis which was present in tissue from the same site nine days after the onset of the reaction. Furthermore, in most instances the lesions described have been demonstrated in experimental animals receiving the drugs as well as in clinical material.^{122,128}

The belief that the lesion described represents allergic reactions rather than pharma-

cologic or toxic effects of the drugs is based upon several lines of evidence. The lesions attributed to sulfonamides and other drugs are in most cases similar to those found in serum sickness or experimental protein sensitization with typical immunologic findings. When adequate clinical evidence was available, most of the patients in whom pathologic lesions were described have shown typical manifestations of drug sensitivity such as drug fever, skin rashes, arthralgia and asthma during life. The period of administration of the drugs was adequate to produce sensitization but the doses given were not excessive and the degree of reaction bore no relation to the doses used. In many instances, more than one course of the drug had been given and several patients developed reactions from doses smaller than those that they had previously tolerated without untoward symptoms. There is, therefore, good evidence that the histologic lesions are produced by drugs and that they represent sensitization rather than toxic effects. However, as Klemperer,⁷ Selye¹²⁹ and others have pointed out, these tissue changes can scarcely be considered conclusive proof of allergy in the absence of corroborative clinical and immunologic evidence.

In addition to the lesions mentioned, many writers have considered the massive parenchymal necrosis (acute yellow atrophy) of the liver produced by such drugs as cinchophen, sulfonamides and arsphenamine as a sensitization phenomenon. More, McMillan and Duff⁶⁶ considered massive hepatic necrosis due to sulfonamides and the mild focal necrosis, which involved the liver coincidentally with many other organs, as different degrees of the same process and described patients showing intermediate stages of liver damage.

The characteristic change in the bone marrow noted in agranulocytosis due to drugs, an arrest of maturation of myeloid elements at the stem cell stage, may occur in association with the foci of necrosis which are considered a part of the sensitization

picture⁶⁶ but the relation between the two processes has not been established.

DIAGNOSIS AND MANAGEMENT OF DRUG ALLERGIES

From the discussion of the immunologic features it is apparent that the diagnosis of allergy to protein drugs and vegetable gums can usually be made by means of suitable skin tests but that skin tests and antibody determinations are not reliable in the diagnosis of allergy to crystalloid drugs. Patch tests are frequently of aid in establishing the cause of certain types of skin reactions and positive intracutaneous tests may be obtained with a few crystalloids such as thiamine but usually the diagnosis of allergy to drugs of simple chemical structure must be made on clinical grounds. The most important factor is a knowledge of the diverse manifestations of drug sensitivity, of the symptoms most commonly produced by each type of drug and of the time during the administration when they are most apt to appear. For example, the sudden occurrence of fever, with or without leukocytosis, during the second week of sulfonamide therapy should immediately suggest drug fever and the drug should be discontinued or penicillin substituted. The precautions to be observed with various types of drugs need not be presented here in detail; if the physician is alert to the possibility of drug allergy, a presumptive diagnosis is rarely difficult. Except for the reactions manifested by asthma, rhinitis or urticaria, the drug sensitizations are not notably more common in persons with hereditary predisposition to allergic diseases and the presence or absence of a past history of such diseases is not an important factor in their diagnosis.

The first step in handling any drug allergy is to discontinue the causative drug and in many cases no other treatment is needed although the more serious manifestations of idiosyncrasy, such as agranulocytosis, hepatitis and exfoliative dermatitis, require in addition symptomatic and protective treatment. Occasionally, especially in the case of penicillin, if the allergic

symptoms are mild and the indications for the drug are very strong, its continued administration may be justified but this should be done only with a knowledge of the reactions of the particular drug and with careful observation of the progress of the manifestations of sensitization. The same is true of further use of a drug after the patient has reacted unfavorably in a previous course of treatment. When no acceptable substitute is available, the only reliable index of persisting sensitivity (except in the case of protein drugs) is a small test dose administered by the usual route. It has already been noted that penicillin sensitization is one of the most transitory of drug allergies but at least one death has been attributed to an attempt to use penicillin in a patient who had previously showed evidence of sensitization.¹³⁰

Several authors have attempted to desensitize patients with a drug allergy by gradually increasing doses of the causative drug.^{36, 51, 131, 132, 133} While the procedure has frequently proven effective in the case of heterologous sera and other protein drugs, the evidence of desensitization to non-protein agents is less convincing. Attempts at oral desensitization of patients with contact dermatitis due to sulfonamides have produced fever and constitutional symptoms, accompanied by marked eosinophilia (leukocyte counts of 16,000 with 62 per cent eosinophiles⁵¹) which may well have been evidence of serious visceral damage. In the present state of knowledge, the theoretical danger of such a procedure outweighs the evidence of its practical value.

There is some clinical and experimental evidence that the incidence of development of contact dermatitis from the external use of a drug is lessened by the previous or simultaneous oral administration of the same drug.^{54, 134} The practical significance of this phenomenon has not been developed.

SUMMARY

Allergy to drugs is very common and its manifestations vary in importance from transitory skin eruptions to fatal reactions.

Among the symptoms which are considered due to sensitization are not only the usual allergic symptoms of asthma, rhinitis, urticaria and angio-edema but drug fever, leukocytosis, arthralgia, lymphadenopathy and many types of skin eruptions. There is also considerable evidence that hepatitis, agranulocytosis and thrombocytopenia due to drugs are phenomena of sensitization rather than of primary toxicity. In sensitization due to protein drugs, circulating antibodies are usually demonstrable and skin tests are of value in diagnosis. In cases due to the non-protein drugs, antibodies are rarely demonstrated by the usual methods and skin tests, except for patch tests in certain types of dermatitis, are of little diagnostic value. Pathologic studies have demonstrated widespread visceral lesions, chiefly arteritis and focal necrosis, in patients who showed clinical evidences of drug sensitization. The diagnosis of drug allergy depends primarily on a knowledge of its diverse manifestations and of the symptoms most commonly produced by each type of drug. The degree of specificity and the duration of such sensitizations are so variable that generalizations are impossible. Desensitization with protein substances is often successful but the results of similar attempts with non-protein drugs are inconclusive.

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A Working Classification of Asthma

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IN general, there are two ways of approaching the study of chronic disease: In one the investigator selects a few representative cases and then studies these from every possible angle so as to discover and evaluate every deviation from the normal anatomy or physiology which they might display. In the other, the student stands at a distance to try to see the disease as a whole, to compare the "pictures" presented by different groups of patients, to see what these groups have in common one with another and then to see whether the differences between them are real and substantial or whether they are merely variations in the degrees with which the different patients react to this or that aspect of their illness; in other words, to see whether the differences as observed are qualitative or merely quantitative. The fact is that in practice these two ways of approach are not separated too sharply. The "representative case" cannot be selected without some knowledge of the whole disease and groups of patients cannot be evaluated without knowledge of certain details. In his study of asthma so far, the author has devoted his attention mostly to examination of the different over-all "pictures." The fact that he has changed his ideas of classification from time to time is not surprising; it indicates that the problem is not easy and it strengthens his belief that, so far at least, time has not been lost by postponing the intensive investigation of "a few representative cases." To the author a working classification of all the patients who wheeze seems essential. The latest edition of this working classification appears to be so useful, both in the clinic and in the laboratory, that it is presented and discussed here. (Table I.)

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A WORKING CLASSIFICATION OF ASTHMA

The asthma which begins before age thirty is a different disease from the asthma which begins after age forty. The picture presented by the "young lady" who wheezes for a day or two when her ragweed hay fever

TABLE I A WORKING CLASSIFICATION OF ASTHMA	
Asthma Begins before Age 30	Asthma Begins after Age 40
"Extrinsic" (Allergy)	"Intrinsic"
Simple	Bacterial Allergy (hard to prove)
Diagnosis easy by history	"Depletion"
Complicated by infections by "depletion"	Psycho—Fatigue
"Asthmatic Bronchitis"	Somatic
Vasomotor rhinitis leads to asthma (often severe)	Infection { Sinuses Bronchi Teeth Other
	Malnutrition
	(Note Selye's "Alarm Reaction")
	"Polypoid Sinusitis"
	Emphysema { Functional Structural
	Tumors and Foreign Bodies

becomes severe is quite different from the picture presented by the "old gentleman" who is "depleted" by the exigencies of a hectic career in business and who finally succumbs to an infection which thereupon precipitates asthma which persists as a chronic, debilitating, serious disease. At the moment of admission to the hospital these two individuals have much in common. They both wheeze and in both this wheeze is relieved by epinephrine. Examination and x-ray in both cases will show the diaphragm low, the lungs distended. In both, the eosinophile cells in the blood may be increased. A "stuffinosis" may be present in both. The immediate pictures are much alike. They both have "asthma." It is the

over-all picture which varies so widely. The histories, treatment and prognosis are utterly different in the two cases.

When asthma begins before age thirty its cause should be considered as allergy until proved otherwise. By allergy is meant a clinical sensitiveness to some foreign substance, which occurs usually in the form of a dust, but may in a few cases occur as a food or, rarely, as a drug. The symptoms develop because of the reaction which results when the patient makes contact with this foreign substance. The great majority of young people who develop asthma before age thirty will tell in their history that the asthma occurs only at certain times of year and/or only in certain particular environments. Some of them know that their asthma is merely a complication of hay fever and all they want is treatment to prevent the next season's attack; others know that cats, dogs or horses are intolerable and they, too, want protection against attacks which occur in odd places and at odd times to make life a burden. Other cases, however—and they constitute the great majority—are not aware of their allergy. It is only when the physician unravels the long story by noting the dates and ages when each and every attack began and when it ended, and by noting at the same time the relation of attacks to changes in residence, in occupation, or perhaps to the time of year, that the nature of the process becomes clear. As the table says "diagnosis easy by history"; it should be easy but there are tricks in history taking and the physician who would treat asthma must be a detective as well as a doctor.

This simple allergic process may become "complicated." In many cases the attack continues after exposure to the foreign substance has ended. Secondary infections are the common factors; a pharyngitis or sinusitis can cause the symptoms of a ragweed hay fever to continue into late October, past the time when the simple cases have cleared. An infection can make the attack started by the visit to grandma and her cat hang on for a week or so after the

boy has returned to his home. "Depletion" by itself and without clear evidence of infection can complicate a simple allergic asthma, but that will be discussed later. In all these cases in which allergy plays such a vital rôle it is the clinical history which reveals the cause of the trouble. Skin tests usually confirm the history; but if they remain negative when the patient ought to be sensitive, the history should be the guide, at least until proved to be wrong. The reason for this is that skin tests which are negative at first may become positive later. The sensitiveness of the skin may or may not reflect the sensitiveness of other tissues. In a few difficult cases the finding of skin tests positive to substances chosen at random will suggest some new factor the importance of which will be disclosed by further history and observation. In general, one can say that in the young extrinsic cases the theory and mechanism of allergy provides an adequate explanation of the clinical pictures observed: It makes sense!

"Asthmatic bronchitis" is a designation which is useful for it applies to a goodly number of cases. The term has been used too loosely; it should apply to those cases only whose asthma comes in isolated attacks at long intervals apart and without change in the home or occupational environment, the attacks being precipitated by head colds and bronchitis. The two words indicate the mechanism. The new infection—the "bronchitis"—not only starts the process but it alters the sensitiveness of the individual. Why do these people wheeze with their colds? Is it not because the new infection lowers the threshold of reaction to make a slight degree of sensitiveness or allergy become effective enough to cause clinical symptoms? The support for such a theory comes from the considerable number of patients, especially young people, in whom it seems to apply. Also, the results of treatment fit the theory. When the general health can be improved so that resistance to new respiratory infections is increased, then the attacks are prevented. The rôle of allergy—the "asthmatic" factor—is demonstrated by

a number of cases in which removal of the offending factor, the cat, the feather pillow or the cosmetic, resulted in the removal of the "asthmatic" factor. New colds persist as usual but now there is no wheeze to go with them. In occasional cases specific treatment to desensitize the individual against the particular foreign substance—cat hair or dog hair, for example—will modify his reaction capacity to a considerable extent. The author must acknowledge that proof of the theory that the threshold for allergic reaction can be lowered in various ways has not yet been demonstrated by animal experiments in the laboratory. Present support derives entirely from observations in the clinic. The treatment of asthmatic bronchitis is not always easy.

Vasomotor rhinitis leads to asthma. There is a small number of patients who develop a chronic vasomotor rhinitis in their twenties; most of them are women. Evidence of allergy is not to be found; the symptoms are remarkably persistent, bearing no relation to changes in season or environment, and skin tests show no reaction to any common food or dust substance which will make sense with the history or with the subsequent experience with that patient. For some time, usually several years, the nasal symptoms continue in a peculiarly distressing manner and then quite suddenly asthma develops and, like the nasal symptoms, this asthma is persistent and is often severe. As a whole, these patients are hard to deal with; no treatment is really satisfactory and in some the asthma goes on until it becomes intractable. One or two of these patients, young women in their late twenties or early thirties, have died in status asthmaticus and at autopsy have shown the typical pathological condition of death from asthma with the bronchi occluded by tough, sticky exudate and the lungs distended. Whether this general picture represents a separate disease or whether it is merely an exaggeration of other more common types of asthma is uncertain. The subject is important and requires much further study.

When asthma begins after age forty the cause is not allergy unless proved otherwise. Allergy is a disease of youth. The age at which typical allergic asthma begins and the age at which typical ragweed hay fever begins is usually around age twenty. After that the curve which summarizes the ages of onset falls off until after age forty; there are only a few individuals who begin their symptoms at an older age. The "old gentleman" is not affected by changes in environment, at least so far as specific dusts are concerned, and he is not sensitive to any particular food. Whatever the cause of his trouble, it is something which he carries with him. Unlike the "young lady" whose asthma clears promptly after admission to the clean and relatively dust-free hospital ward, his asthma continues; his response to treatment is slow. What is the nature of this disease which is "intrinsic" in so far as the cause is "inside" the body?

Infection plays a part but this varies and, as will be seen, the evidence of infection is not clear in many of the cases. "Bacterial allergy" is the obvious concept but it is hard to prove. Skin tests with bacteria and their products, like toxins or vaccines, will elicit positive reactions but these are, like the tuberculin reaction, delayed in appearance and inflammatory in nature. Like the tuberculin reaction, they indicate that this individual has or has had infection with the organism. As with the tuberculin reaction itself, the test finding has little practical significance except as an interesting item to be evaluated in a few cases under special investigation. Such skin tests do not help in the study of asthma. In contrast to tests with toxins and whole organism suspensions (vaccines), the specific soluble carbohydrate substances derived from the capsules of certain bacteria can elicit a skin test of the immediate, urticarial wheal and erythema type. This occurs, however, only when antibodies for the organism are present in quantity. It is possible that further studies with specific bacterial carbohydrates will be helpful; the problem will be concerned with the relations between the skin results and the state of the

asthma, a study of immunology involved. It may be that bacterial allergy can be defined and found to be important.

"Depletion" is a factor in the cause of asthma which has more than casual importance. The toxins arising from a focal infection can perhaps cause a tissue injury to make the cells release histamine and so cause asthma by a mechanism comparable to that of the antigen-antibody reactions. The case for chronic infections is understandable. The case for certain intoxications, as with sulfonamide drugs, is also understandable. Other conditions, however, like malnutrition, improper hygiene and, in particular, the larger group of psychic disturbances which are so poorly defined are not so easy to correlate with the other pictures of asthma due to more orthodox causes. Do they also produce asthma through tissue injury and histamine release? There is evidence to indicate that this happens but it is not clear; the problem needs much more study.

Selye's conception and investigation of the diseases of adaptation is pertinent to this problem even though some of the physiologic changes—the fall in blood chloride, for example—which he finds after injuries is not found also in our patients with severe asthma. Whether the discrepancy depends upon quantitative rather than qualitative factors, or whether the chronic shock-like state which develops after injury finds its counterpart in the depletion of severe asthma remains to be disclosed. In this latter case the depletion is the result of the process. It is our clinical observations which point to the fact that depletion started perhaps by a primary injury either of the soma or of the psyche that may be the cause of the process.

Can "depletion" of one sort or another cause asthma without allergy or without infection of any kind? That is the important question and again it is clinical observations which have provided the basis for the answer. It is the end results of treatment prescribed and administered on a basis of depletion rather than of allergy or infection

which indicate a true cause and effect relationship. Figure 1 shows a sample of twenty-three patients with intrinsic asthma who have been "cured." The sample has been taken at random; the cases are not selected on any basis except for the final "cure." The figure shows that "cure" may persist for ten years or more but it is the method of cure as evaluated by both doctor and patient which is the important item. In some cases treatment with potassium iodide or the removal of bad teeth has explained the "cure" and that of course does indicate infection; but when asthma clears when the bad hygiene is improved or when the malnutrition is corrected by proper feeding, and especially when it clears after the elimination of psychic difficulties—"the divorce was finally arranged"—one has to recognize that the problem includes other factors beside allergy and infection. The author finds that these cases are common. It is in these cases that treatment of the patient is so much more important than treatment of the asthma. There is much to learn about psycho and psychosomatic factors in this chronic disease.

Polypoid sinusitis with asthma is given a separate heading chiefly because the patients to be included are such a large group. Lesions of the nose and sinuses are noted in three places in this classification. The chronic vasomotor rhinitis which develops in young women has been mentioned. Some of them have polyps, an extension and result of the chronic irritation of the sinus membranes. In chronic intrinsic asthma, occurring in older patients, polypoid sinus disease is common; it is found in about one-third of all the cases and the typical subjects are grouped in this special designation. Operation on the sinuses does more harm than good, except in a few "lucky" cases, and it is interesting to speculate on these few. Under the heading "Depletion," Table 1 indicates infection of the sinuses as one of the subgroups, and in so doing it implies that treatment of the sinusitis by operation and removal of the focal infection has brought relief to the

asthma. Can we say, therefore, that chronic infection of the sinuses does occur, but only in a few cases, and that in the other group which is much larger the polypoid sinusitis represents a part of the picture and not a

of a patient whose frontal sinuses were opened from above through the base of the skull and the cultures showed no growth. How to distinguish the few cases in which drainage of the paranasal sinuses will relieve

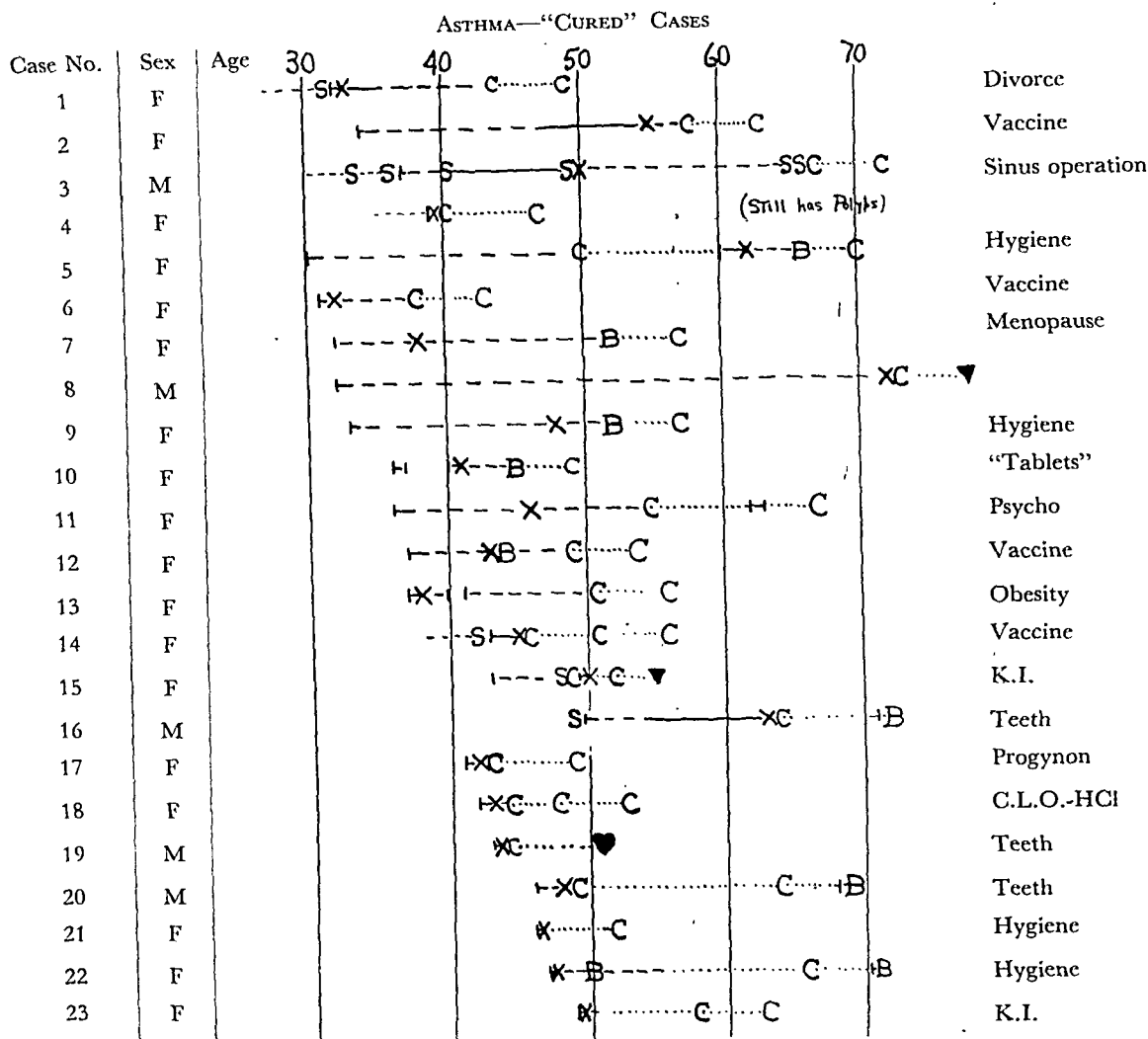


FIG. 1. A random sample showing twenty-three cases of "cured" asthma is presented to show the general method of study. Each line represents the life history of the patient's asthma. On the left, a vertical mark indicates the age at which the asthma began and the dashes or the continuous line show whether this asthma was in attacks or was persistent. Symbols in the line indicate as follows: "X" marks the first visit of the patient to the author; "B" means better, the asthma under control. "C" means cured, the patient free of asthma without treatment and the dotted line after "C" or sometimes before it indicates the duration of this "cure." New letters, whether "B" or "C," indicate a new follow-up report. "S" means sinus operation which sometimes, as in cases 1, 3 and 14, was made before and not after the onset of asthma. In cases 16, 20 and 22, the asthma recurred at about the age of 70 but the "B" indicates that it was not severe. The black triangles indicate death from causes other than asthma. The black heart indicates death from coronary occlusion. The circles around the small initials in the left column indicate the men; there are five men in this list. The words in the right hand column indicate the method of "cure," as explained in the text.

cause of it? When in earlier days these other patients were operated upon, the cultures taken from the sinus content, a thick white mucoid material, often showed no growth. The author recalls the autopsy

the asthma permanently from the vast majority in which similar treatment will make the asthma worse (after a very temporary benefit) is one of the pressing questions.

Emphysema causes wheezy breathing (asthma). Every attack of asthma, no matter what its cause, is accompanied by a "stretching" of the lungs; the chest enlarges, the diaphragms become flat and low and their movement is restricted. The vital capacity falls off. As the attack passes, the emphysema passes also; it is a purely functional emphysema. Structural emphysema is probably a definite disease entity. It has been called idiopathic because it develops without cause, insidiously in older people and more in men than in women. It is a slowly progressive disease and has a poor prognosis. The victims do not survive for more than a few years. Physical examination shows changes much like those of chronic asthma and the diagnosis depends more on the history and the subsequent behavior. The relation to exertion is always sharp. At rest the patient is reasonably comfortable but his tolerance for exercise is small. A point of diagnostic importance is that whereas the patient with asthma has bad nights, "emphysema sleeps well." Mention of the disease is included here because it happens not infrequently that patients with structural emphysema are put through the asthma routine, with skin tests to many different substances and sometimes treatment with dust extracts and other materials. The fact that such treatment does no good is not surprising; it reflects the lack of training and insight of the attending physician.

Tumors and foreign bodies must, like emphysema, be mentioned in every survey of the asthma problem. Adenoma or carcinoma of the bronchus, gumma of the trachea, Hodgkin's disease involving the peribronchial lymph nodes and sarcoid have all been seen by the author in patients who were thought to be asthmatic. Merely to think of these possibilities is usually enough to rule them out but it is important to think of them.

SUMMARY

1. A working classification of some sort is essential for the study and treatment of asthma.
2. When asthma begins before age thirty, it should be considered to depend upon allergy until proved otherwise.
3. When asthma begins after age forty, it should be considered as due to factors other than allergy until proved otherwise.
4. In the younger age group it is the clinical history which is of vital importance in diagnosis and so in treatment.
5. In the older group the factors of "depletion," both psychic and somatic, may be essential.
6. Polypoid sinus disease is more a part of the picture than a cause of it.
7. Structural emphysema as well as tumors and foreign bodies must be considered in all difficult cases.

Recognition of Emotional Factors in Allergic Manifestations*

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THE literature relating to causes of allergic reactions refers not only to specific causes but also makes constant reference to non-specific causes, under which are grouped most prominently "worry, nervousness and fatigue." The frequency with which these non-specific causes are mentioned and the generally acknowledged rôle that they play, not only in precipitating and aggravating allergic reactions but even at times acting as sole causative agents, suggests that a closer survey and appreciation of the patient's history would prove fruitful, particularly if attention is directed to the emotional and environmental circumstances under which the allergic disorder first became manifest. In many instances, a striking correlation will be found between the onset of subjective complaints and a single psychologic event or series of such events. Conversely, the remission of allergic manifestations may also coincide with the occurrence of severe or disabling emotional experiences. It is of at least empiric value that the Quarterly Cumulative Index Medicus for the past ten years contains articles attributing specific curative properties to a multiplicity of unrelated drugs and equally unrelated procedures. The only common basis upon which these claims may be said to achieve their results is their common suggestive value or perhaps the faith that the patient has in his particular allergist.

It is incorrect to assume that the taking of a psychiatric history is the exclusive right and privilege of those engaged in psychologic medicine. This misconception,

which is widely held, stems from the intensive specialization in the increasingly numerous branches of medicine. The medical profession seems to have progressed to the point where it now resembles the many factional units of a complex labor group. There is no valid reason why history taking should rigidly avoid obtaining an account of the personal and intimate history of the patient in terms of psychologic events and integrating these events with the somatic reactions which occurred at the time. There is no longer any doubt that when the physician combines the physical approach to a problem with an appreciation of emotional factors he establishes with the patient a contact or rapport which has great therapeutic potentials. This rapport, once established, is sometimes sufficiently strong in itself to alleviate distressing symptoms and on occasion it has positive curative value. For example, the allergist who is convinced by his own faith in the efficacy of his particular mode of therapy not infrequently is so forceful and energetic in his approach to the patient's problem that an alteration may take place in the patient's underlying emotional conflicts. The immediate improvement in the patient's condition is then attributed to a specific administration rather than to the personality of the administrator. The results thus achieved may possibly explain why the faithful exponents of foods as allergens, house dust as an allergen or even sodium chloride as an allergen are so vigorous in supporting their respective claims in the universality of their treatments.

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By placing prime importance upon the history of the patient's family (rather than upon his personal, psychologic history) and searching for clues of related allergic manifestation in members of his immediate and remote family the allergist emphasizes his primary interest in the fact that allergic disorders are more commonly found in individuals who are constitutionally endowed with physical properties susceptible to specific allergens. From a psychiatric point of view it is proposed that the manner in which the patient's combined psychophysical makeup will respond to various emotional factors will depend upon the extent to which such factors are similar to or in common with those in the patient's particular emotional environment. If this point of view is kept in mind in history taking, it will be necessary to give equal consideration both to inherited intrinsic antibody-antigen reactions and to the patient's emotional reactions to everyday living and activity. It would be unfruitful at this level of knowledge to argue the relative weights and values of these respective elements. In fact, it does not make much difference so long as we bear uppermost in mind the welfare of the individual who is almost constantly distressed by his annoying symptoms.

The personality of the allergically susceptible individual is commonly characterized by emotional immaturity, relative passivity and need for dependence upon some authoritative yet kindly person. The reactions of this type of personality are thus essentially infantile. It is misleading, however, to assume that these traits are characteristic of and peculiar to the allergic individual alone for similar traits are also recognizable in gastrointestinal neuroses and are common in the chronic alcoholic. In view of these widely divergent physical reactions in relatively similar types of emotionally immature persons, it would appear that the choice of physical reaction to an emotional situation bears a relationship to the patterns of living and behavior of the parents of the emotionally immature individual as well as to his physical makeup.

The outstanding and provocative elements that give rise to many if not all adult maladjustments have their origin in the interaction of the various members of the family unit. The child's position in the family constellation is constantly threatened by anxiety-provoking situations. The rivalries and resentments common to everyday competition in the home create an emotionally conflictual situation. French¹ has shown that when the conflictual situation involves a threatened or actual loss of love of the mother, or the mother-substitute, the patient responds in a physical way compatible with his inherited constitutional endowments. An example is the often repeated observation that asthma is apparently hereditarily transmitted from the mother. The adolescent, or the patient in a state of emotional turmoil, identifies himself with the mother and behaves in a manner similar to the mother's behavior in order to ward off the threatened withdrawal of love, dependence or the threatened loss of security. It is acknowledged without question that sensitization is transmitted but the point emphasized here is that the sensitization can be utilized for the physical expression of an emotional situation. The behavior of the patient may be characterized by the statement that the emotional tension is expressed in "allergic language."

The trying emotional situations that confront the adolescent or the adult are merely repetitions, in a more complex form, of the same problems that confronted the individual in childhood. The failure to achieve scholastic recognition, the frustrations of a competitive occupation or profession or the threatened dissolution of a marital union are but a few of the many problems that were encountered in a simpler form during the period of childhood development.

It may be judged from the type of material seen in a general psychiatric practice that the allergist, in following a limited restrictive type of therapy and searching for a specific sensitization, is frequently led astray by his contact with a group of symptoms simulating an allergic disorder.

When no results are forthcoming, the symptom complex is given the euphemistic title of "intractable allergy." It is just this group of disorders, in which the provocative factors are most frequently of an emotional character and in which the major, if not the sole, approach should be from a psychologic level.

Particular mention should be made of the frequency with which hyperventilation with its protean manifestations, either in the presence or absence of allergic sensitization, produces a clinical picture that in many instances defies differentiation from an attack of allergically induced asthma.² The anxious, tense, emotionally immature individual is intensely susceptible to changes in his acid-base equilibrium and the outstanding clinical symptom is an inability to breathe. This inability to breathe is predominantly inspiratory and the suddenness of the onset, the complaints of panic and wild gasping for breath may be and often are mistaken for signs of an asthmatic attack. It has been demonstrated that the hyperventilation phenomenon, aside from a few rare instances, is induced by emotional conflict. The management of hyperventilation by a technic other than psychologic then only leads to a state of chronicity and invalidism.

CASE REPORTS

CASE 1. M. H., a twenty-six year old, white, single engineering student was referred for psychiatric consultation and treatment in December, 1945. The complaint was "disabling headaches" of six years' duration. A usual attack was ushered in by a sharp, boring pain, beginning on either side of the head and later spreading over the whole head and then radiating to the neck, both shoulders and down the spine. Vision became progressively blurred and scintillating lights appeared when vision was practically nil. Nausea and vomiting followed and these were accompanied by anxiety and a vague feeling of guilt. Complete isolation in a darkened room for twenty-four hours usually cleared an attack but the patient would not

fully recover for ten days or two weeks at which time there would be a recurrence.

The patient's symptoms first began to appear in September, 1940 when, while watching a football practice game, he suddenly felt "hot all over," became tense and apprehensive and then his heart "began to pound." This episode lasted for about thirty minutes and that evening he was nauseated. Two days later, while at a movie, he had a similar attack. For a period of a month thereafter he was entirely well until, again at a football game, he became nauseated and had the first of the headaches described.

The results of the physical and neurologic examinations were negative. The usual laboratory procedures, including x-rays of the chest, head, spine as well as the electrocardiogram, revealed nothing unusual. The pneumo-encephalogram showed an incomplete filling and ventriculograms were therefore obtained. The results were considered normal. All types of medication were seemingly of no value in giving any degree of subjective relief. With a family history of migraine in the mother, the patient was referred to an allergist whose physical findings were essentially as stated. He put the patient on an elimination diet. After two and one-half years, during which time he lost 35 pounds, his headaches were about the same in frequency and intensity.

On the recommendation of his physician, he was excused from selective service and went to work in Alaska on a construction project. Away from home for a period of two years, he had only occasional attacks. Upon his return he was advised to give up his plans for an education and take up an occupation in a colder climate.

A more detailed psychiatric study revealed that he was the eldest of four brothers, the youngest of whom was then twelve years of age. The mother outwardly affected a calm and serene disposition but in their home her attitude toward the father bordered on despotic tyranny. The father, chronically alcoholic, was totally neglected by the family and when he attempted to exert authority, generally in a drunken rage, he was simply placated. One form of overt punishment of the father by the mother consisted of periodic headaches that had been diagnosed as migraine. As early as at the age of ten years, the patient utilized transient "sick headaches" not only to maintain his position with the mother in competition with his brothers

but also to immobilize any anger emanating from the father.

At the age of sixteen, he was instrumental in separating the mother and father who were in a violent quarrel and in the argument the father turned upon the patient, administering a brutal beating. The patient stated that he was choked until he thought his eyes "would pop out of the head." Several days later, he awakened from a sound sleep in a very anxious, tense state and "was unable to breathe." Detailed accounts of this "attack" were highly suggestive of prolonged hyperventilation. It was concluded that these physical symptoms set the pattern for his later so-called migraine. To substantiate further this conclusion, the patient was overbreathed for 90 seconds and all of his physical symptoms, accompanied by great apprehension, were reproduced.

Further discussions clarified his intense and almost infantile dependence upon the strong-minded mother. His reactions toward his psychically weak father were those of hate and resentment, both accentuated by the beating his father gave him. In time, his attacks of headache became related to other emotional situations characterized by violence, for example, the football games. He has had no headaches for the past six and one-half months. He has returned to school and is living at home with his mother, father and brothers.

CASE II. R. F., a forty-year old white, married man, who is a general merchant, was referred to the University of California Hospital in April, 1944, for a study of his recurrent, generalized urticaria and angioneurotic edema of two years' duration.

He had lived his entire life in the same township. The routine history revealed no significant factors in his family background or past history.

He was perfectly well physically until April, 1942. He awakened one morning to find his chest covered with "itching hives" about 2 inches in diameter. That same afternoon his eyelids and lips began to swell so that by evening he was hardly recognizable. Sometime during the night all of the manifestations disappeared. Intermittently, he had similar attacks as often as four times weekly and at the time of his hospital entry the urticaria was generalized. He had recognized the fact that emotional situations aggravated an attack and for this reason he had begun to live the life of a recluse.

Prior to admission to the hospital he had con-

sulted several physicians with little or no relief. Apparently, no extrinsic or intrinsic allergic factors were implicated although in one test he was found to be sensitive to corn, peas and grapes. Subsequent tests did not confirm the sensitization. A barrage of medications, including sulfa drugs and penicillin, were used to no avail.

After reviewing the history with the patient the direct question was asked: "What do you think causes your hives"? After some hesitation the patient responded: "These things seem to come on when I get a funny tight feeling in my throat. I get this feeling when I am around my wife, and that is why I stay away from her and the children as much as possible."

In further discussion of the so-called "negative family history" several interesting points were uncovered. The father had died before the patient's birth. He had one brother ten years his senior. His relations with his mother and brother were, to the best of his knowledge, quite amiable until his brother, by legitimate means, took over the controlling interest in the family enterprise. Although the mother was quite complacent, the patient bitterly resented the arrangement and forthwith severed himself entirely from his brother, urging his mother to do likewise. "At least I wanted the satisfaction of caring for her myself," he said.

His mother died when he was twenty-four years of age and one year later he married. In 1939, at the age of thirty-five years, he became associated with his brother-in-law in a business venture that proved highly successful. Some time later, the patient was confronted with certain financial irregularities of the brother-in-law. The patient's wife tended to protect her kin and urged the patient to let it "blow over." From this time on he became increasingly irritable, restless and nervous. He tried to rationalize his nervousness, ascribing it to problems of labor, the war and minor disagreements in the home. In April, 1942, he had his first attack of hives.

When attention was called to the "funny tight feeling in his throat" and his unexpressed hostility toward his brother-in-law, he volunteered the statement that his unhappy relations with the brother-in-law were identical with those he had with his own brother. The relations with his mother, his obvious dependence upon her and his subsequent equivalent dependence on his wife were left undiscussed.

He was in the hospital for six days for observation only and to date has had no recurrence of any urticaria.

CASE III. G. L., a sixty-year old white, married man and business executive, was first interviewed in December, 1944. In 1921, he had his first attack of hay fever and since 1931 had suffered from recurring attacks of asthma. At various times, he had been found sensitive to approximately thirty different pollens, particularly that of Bermuda grass, foxtail and velvet grass. When he originally sought help for his asthmatic attacks, an examining physician on May 26, 1931 noted "worry and nervousness. ++++" The results of the general physical examination and of laboratory tests in 1944 were negative with the exception of the sensitizations just mentioned.

The patient's medical history disclosed that the first treatments aiming at desensitization were poorly tolerated and that after an interval relief was found from "Doctor Tucker's Asthma Specific." In time, this preparation lost its effectiveness and then followed a period of ten years of alternate trials at desensitization and elimination diets. At the patient's own request, he was finally sent to a psychiatrist for an evaluation of his "nervousness."

Given the opportunity, the patient proved most cooperative. In great detail, he gave an account of his most unhappy early childhood. He was the only child of an aged couple. His father, a ruthless, domineering and exquisitely puritanical minister, was forever dwelling upon the wickedness of mankind and the potential sources of evil in his son. The mother vacillated from moods of serenity and compassion, on the one hand, to ominous, threatening domination on the other. He remarked: "I could never know what side of the fence she was on and until her death I was out of breath trying to keep up with her."

From early childhood his feeling and actions had been patterned in accordance with his mother's more sublime wishes. At the age of twenty-two he fell in love with a distant relative and when he sought permission to advance his courtship, he was rebuked and discouraged by his mother's remarks that his offspring would be idiots. In striking contrast to the mother, this girl was soft, docile and "angelic." The disruption of this love affair gave rise to a group of symptoms associated with hyperventilation which, at that time, was interpreted as "a touch

of asthma." The family moved and the so-called asthma cleared.

His marriage at the age of twenty-five was the culmination of an arrangement managed by the mother. The marriage as a source of physical companionship was reasonably successful. As a source of warmth and affection it was a dismal failure. His wife, possessing the aggressiveness of his mother, pushed him into a most lucrative position.

What precipitated his hay fever in 1921 is unknown but the onset of the asthma is definitely related to a visit with the girl of his first love affair. She at that time gave an account of her own unhappy marital experience, described her continued attachment to the patient and pledged unremitting affection for him. Several days after her departure his asthmatic attacks began.

The history was told with a great display of emotion and it was easily recognizable with interpretation that the patient had great dependence upon his earlier love. The importance of the emotional element was further demonstrated by the fact that by merely telephoning or writing to her he had been able to ward off attacks. Of particular interest is that these attacks of asthma were allergically determined; nevertheless, in two and one half years he has had but two attacks and these were treated without resort to adrenalin.

CASE IV. R. E., a thirty-two year old, white, married woman was referred to the University of California Hospital in March, 1939 for psychiatric evaluation. The referring internist was impressed by the patient's behavior in the presence of her mother who had come with her and who seemed more distressed than the patient by the asthmatic attack of which the patient complained.

The patient had been under continuous medical care since she was ten years of age. She had had contact with innumerable allergists throughout the country and had been subjected to every conceivable medication and procedure, including residence in an air-conditioned home prepared at great expense. Her asthma was truly "intractable." The internist had been the first to evaluate accurately the emotional factors involved and, because of the complexity of the situation, the patient was referred for further investigation. In the several contacts the internist had had with her, he had been able, by his interest, to control several of her attacks without medication. At the same time, it was recognized

that she had an allergic susceptibility to certain pollens and foods, particularly eggs and wheat.

The earliest memories of the patient center about an experience at the age of five. As a consequence of disobedience, she said: "I was spanked by my father until I cried so hard that I lost my breath. To bring me back, my mother turned the garden hose full force in my face." An earlier significant event was related by the mother who stated that when the patient was one year old the coughing paroxysms of whooping cough were so severe "that I had to hold her by the ankles and slap her buttocks to start her breathing again." The patient's first attacks of clinical asthma took place after a series of strenuous exercises. At this point her medical history began.

Many pertinent emotional factors were evident in the family history. The mother and father never enjoyed a real degree of harmony. The mother's affections were expended exclusively on an only son sixteen years older than the patient. The patient can readily recall the often repeated remark that she was unwanted and that she resembled her father in personality and temperament. When she was twelve years old, her brother, then twenty-eight years of age, was killed accidentally. The mother, after a period of mourning, reversed her previous attitude toward the patient and showered her with affection so that "mother and I became very close and people remarked on her devotion to me." The attacks of asthma were thereafter less frequent and less intense until her marriage at the age of sixteen to a close associate of her brother. She remarked: "My mother was very pleased with the marriage, but almost overnight my asthma returned in full force."

The patient's premarital plans included recognition of the husband as a central figure in the household but this plan was short-lived since the mother joined the couple on their honeymoon insisting that "sex was the root of her asthma." It is striking indeed that in those instances when separation from the mother was enforced the attacks of asthma were greatly diminished and at times were absent.

The psychiatric discussions brought out the marked dependence on the mother and the equally strong tendency to achieve a degree of independence of her mother. The struggle between these two opposing drives was satisfied

to the extent that the patient retained her mother's affection and at the same time endeavored to punish her mother for her ruthless domination by having the asthma attacks. The patient has been entirely free from attacks of asthma for eight years. During the war years she resided with her mother and since her husband's return from service relations with the mother continue to be amicable.

COMMENTS

Clinical case histories, as reported here, are open to several criticisms. Obviously, the material is selected to demonstrate the purpose of the thesis, namely, the importance of adequate history taking with reference to the emotional factors that are operative in allergic manifestation. Dratler,³ in a critical review of the problem of urticaria published in 1946, states that "the most important source of information for the determination of etiology is the history." He continues: "All authors have stressed that the patient's experience and observations should be more valued than the skin and laboratory tests." To the extent that psychogenic factors are concerned Dratler states that "the psychogenic element is considered as one of the most important factors in etiology." In another recent paper, Harris⁴ gives an entirely different appraisal of the emotions when he states: "In recent years, an old theory and one that most of us considered long ago discarded, namely, that bronchial asthma is a form of neurosis, has been renewed." Harris, with many others, assumes that the emotional turmoil is a natural consequence of an allergic disorder but there is much evidence to question this assumption.

Another criticism is that the diagnoses are in error in that these individuals are "simply neurotic." In this regard, the diagnoses in all the instances cited were made by allergists who treated the patients without success by their restrictive and circumscribed type of therapy. Two of the patients were treated to the point of financial insolvency.

A third possible criticism is that psychiatric interviews are non-scientific and are lacking in specificity in that the therapeutic

results cannot be adequately measured and appraised by rigid scientific standards. However, it seems impractical to await the complete understanding of the mechanism whereby emotions influence bodily function before utilizing the psychiatric approach. In overlooking the emotional components while searching for a specific remedy we are indeed inconsiderate of the patient. Bowman's⁵ remark regarding the neurosis applies equally well to most, if not all, physical diseases: "Treatment should be based on securing the maximum results in the shortest time with the least amount of suffering for the patient."

CONCLUSION

It is concluded that if history taking is broadened to include the psychologic events

of the patient's history and if these events are related to the somatic reactions at the time of occurrence, the rôle of the emotions in causing, precipitating and aggravating latent allergic sensitization will be adequately recognized and the study, diagnosis, treatment and cure of allergic manifestations will be substantially furthered.

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Allergy in the Nervous System*

A Review of the Literature

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IN recent years an increasing tendency has been noted in neurologic clinics and meetings to ascribe to allergy an important rôle in the etiology of measles encephalitis, scarlet fever encephalitis, multiple sclerosis and some other nervous diseases. Especially in those forms of encephalitis in which there is loss of myelin, an allergic reaction of some kind has been suspected as the common factor producing the break-up of the myelin sheaths.

CLINICO-PATHOLOGIC STUDIES

Osler,² in 1889, added the third case of hemiplegia following vaccination, giving credit to Heine¹ in 1860 and Wuillamie in 1882 for reporting the first two. In addition, Osler noted that cerebral palsies "may follow any of the specific fevers." According to Pollet,⁹ Englemann³ in 1897 noted peripheral neuritis following the use of serum and Gardere and Gangolphe⁴ noted neuritis during the treatment of a case of tetanus by serum therapy in 1908. Optic neuritis during serum sickness was observed by Mason⁵ in 1922. May⁶ in 1923 noted attacks of unnatural somnolence of anaphylactic origin. Sternberg²⁷ also drew attention to seasonal somnolence as a possible form of pollen allergy.

In 1926, Kennedy⁷ suggested that acute perivascular edema of the brain may play a part in some of the malignant types of insular sclerosis. In 1926, Duke⁸ suggested that peripheral nerve lesions may result from food allergy. Hurst²⁹ gave credit to Glanzman¹⁰ as the first to suggest, in 1927, that allergy might be a factor in causing demyelination of the nervous system.

Kennedy¹¹ in 1928 reported meningeal and focal brain disease causing hemiplegia, aphasia, hemianopsia and severe papilledema during the course of serum sickness. Allergic headache due to food was reported by Eyermann¹² in 1930. A case of polyneuritis due to typhoid vaccine was reported by Dr. Geo. H. Hyslop and was described by Kennedy¹¹ in 1928. Typhoid vaccine and staphylococcus vaccine were also reported by Young¹³ in 1932 to cause peripheral neuritis. Winkelman and Gotten¹⁵ reported two cases, one with autopsy findings of encephalomyelitis following the use of serum or vaccine. The autopsied patient had received horse serum seventy-two days previously but had also had symptoms of an upper respiratory infection three weeks later. At autopsy there was inflammation with lymphocytes in the meninges and about blood vessels, especially in the spinal cord, with obliteration of the gray and white matter, congestion and an increase in astrocytes. There also was degeneration with focal necrosis and Gitter cells especially in the cerebrum. Gayle and Bowen¹⁴ reported the case of an eighteen year old boy who developed an acute ascending polyneuritis following the administration of typhoid vaccine and condensed the available autopsy reports in the literature suggesting the following fundamental lesions: peripheral neuritis, destruction of anterior horn cells and focal destruction throughout the brain.

A case of encephalomyelitis following vaccination against yellow fever was described by Lhermitte and Fribourg-Blanc¹⁶ in 1936. This case came to autopsy fifteen

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months after the illness in the nervous system began and so resembled multiple sclerosis clinically and in the pathologic lesions that it strongly suggested to one of us²⁴ that allergy might be a cause of, or a mechanism in, the production of multiple sclerosis and that allergy might be the common factor underlying the breaking up of myelin in all demyelinating diseases of the nervous system.

In 1936, Kennedy¹⁷ suggested that multiple sclerosis should be studied from the standpoint of allergy. The most interesting case that he reported was that of a physician who was sensitive to pork, suffered from recurring eczema and retrobulbar neuritis with a cerebellar seizure and a slight hemiplegia with homolateral severe thalamic sensations after "inadvertently crossing the pork-line," as the patient himself stated.

In 1938, Pardee¹⁸ reported a case of violent convulsions due to ingestion of chocolate. Clark²² described cases of convulsions from foods in 1939.

Finley¹⁹ in 1938 wrote a paper of great interest dealing with encephalitis occurring with vaccination, variola and measles. This paper, coupled with the case of encephalomyelitis described by Lhermitte and Fribourg-Blanc,¹⁶ suggested further the idea that "allergy . . . is . . . an important factor in the pathogenesis of encephalitis associated with vaccination, variola, and measles." Ross²⁰ in 1939 described allergic response to honeybee stings. Baer and Sulzberger²¹ in 1939 studied a group of forty cases of multiple sclerosis from the point of view of atopy. Their comment and conclusions in part follow: "In our opinion and experience the incidence of atopic sensitivity found in this group of cases of multiple sclerosis is little higher than that which is to be expected in any equivalent unselected group studied by the same methods." This, of course, has been the experience of most neurologists but such a conclusion, as they themselves admit, adds nothing for or against the hypothesis that some sort of antibody-antigen reaction may

be the factor responsible for the initial breakup of myelin in this disease.

Winkelman and Moore²³ in 1941 reviewed the literature on "Allergy and Nervous Diseases" and showed the increasing importance placed on allergy in the etiology of many nervous and mental diseases. They presented cases of migraine, epilepsy and focal lesions of the brain in which the clinical picture has been best explained on an allergic basis. Rich²⁶ in 1942 discussed the rôle of hypersensitivity in periarteritis nodosa. Scarlatinal encephalomyelitis has been described by Winkelman.²⁵ One case showed a diffuse inflammation with perivascular necrosis which he interpreted as possibly due to a virus which was dormant in the central nervous system and which "was stimulated by the streptococcal infection. Ferraro²⁸ reported two other cases and interpreted the perivascular inflammation with microglia proliferation and vascular changes as an allergic response.

Hurst²⁹ in 1944 wrote a comprehensive review of demyelinating diseases of the nervous system but seemed to doubt that a relation exists between allergy or anaphylaxis and demyelination. In summary, he said in part, ". . . The known antecedents of demyelination and the means by which it may be produced experimentally are very diverse, and appear to include no common determinant more narrowly specific than injury to the white matter of one type or other. . . . Demyelination appears to be the response of the white matter to injuries short of those immediately lethal to the tissues." Cooke³⁰ has recently summarized most of the knowledge pertaining to allergic neuropathies.

Although the numbers involved are small, the development of a "multiple-sclerosis-like" disease in four of seven workers engaged in research on the disease "swayback" in lambs,⁶⁰ hitherto regarded generally as due to copper deficiency, is very suggestive that there is some common factor between the two diseases. Whether this factor is a virus, a toxin, a deficiency or an antigen is, of course, not known.

STUDIES ON EXPERIMENTAL ANIMALS

The experimental analysis of allergy in the nervous system may conveniently be divided into two parts: (1) encephalomyelitis produced by vaccination or immunization with nervous tissue and (2) diseases of the nervous system produced by other mechanisms, such as the Arthus phenomenon and passive immunization with anti-brain or Forssman antibodies.

Hurst³⁴ in 1932 reviewed the literature concerning paralytic accidents occurring in man following anti-rabies therapy and in experimental animals following injections of brain. Numerous experiments had been performed beginning in 1898 using rabbits, rats and dogs which were given injections of aqueous suspensions of ox, rabbit, human and monkey brain and various types of anti-rabies vaccine. Paralysis were relatively infrequent but the best of these experiments provide interesting data, notably the reports by Miyagawa and Ishii,³¹ Koritschoner and Schweinburg,³² Stuart and Krikorian³³ and Hurst.³⁴ In general, the pathologic picture was inconstant, varying from nothing to explain the paralysis to moderate perivascular inflammation throughout the brain and leptomeninges. Additional changes in neurones, myelin sheaths, axis cylinders and glia were described by Miyagawa and Ishii³¹ but the lack of correlation of so many changes prohibits adequate interpretation of their findings. However, concerning the nature of the antigen, it was found that rabies virus or toxin was not necessary but that the active paralyzing agent was present in aqueous suspensions of normal brain.

Although the opinions of various workers analyzing the experimental^{33,55} and clinical^{48,49} aspects of the problem differed somewhat, it was also found that the antigen probably could be partially destroyed by phenol and heat. Concerning the mode of action of the antigen, it is also of interest to note the following hypotheses: There was an inherent predisposition of the individual to the disease; the injections of brain were not directly toxic but were one of several

means of activating some unidentified latent factor or factors.

Rivers and Schwentker⁴¹ extended the experiments of Rivers, Sprunt and Berry³⁸ by producing paralysis in monkeys more regularly with more prolonged courses of injection and by finding demyelination on microscopic examination of the central nervous system. Ferraro and Jarvis⁴⁷ repeated these experiments almost exactly and thus established the disease on more precise neuropathologic grounds. Concerning the antigen, it is to be noted that its nature had been complicated by the addition of an alcoholic extract to the aqueous suspension. Concerning the mode of action of the antigen, only the allergic theory had come into ascendancy. Thus, there was a pause important in consolidating the findings into a coherent picture although at the expense of a complicated and prolonged technic.

By no means have all experiments along these lines been successful. Hurst²⁹ injected suspensions of human brain and alcoholic extracts of rabbit brain into monkeys and suspensions of pig brain into sheep and lambs repeatedly over a period of one year without producing any disease. Innes and Shearer⁵⁰ injected suspensions of rabbit brain into sheep and lambs three times a week for one year also without producing any disease.

More recently Morgan,⁵⁸ and independently Kabat, Wolf, and Bezer,⁵⁹ by using special adjuvants have produced paralysis in monkeys regularly and rapidly following a single or only a few injections. Several antigens have been used, in general the effectiveness paralleling the myelin content, except for peripheral nerves which failed to produce the disease.

There has been much speculation as to what portion of brain is the antigenic material responsible for allergic encephalomyelitis. From the evidence at hand, it is suggested that the following materials extractable from brain are antigenic (really hapten in nature in that they react with specific antibodies but do not stimulate the

production of antibodies unless combined with a suitable adjuvant):

1. Purified but as yet unidentified material soluble in cold alcohol.^{37,39,40,44}

2. "Protagon," soluble in hot alcohol but insoluble in cold alcohol;⁴⁴ composed of a mixture of sphingomyelin and galactolipins.⁴⁵

3. "Sphingomyelin."⁴⁴

4. "Neurokeratin," soluble in water but insoluble in all common solvents, and present in bacterial cultures on brain-broth.⁵²

5. Material present in aqueous suspensions of gray matter but as yet not further identified.^{40,44}

There is, unfortunately, no evidence that allergic encephalomyelitis is caused by any of these five fractions, although the "alcohol-soluble hapten," "protagon" and "neurokeratin" are more concentrated in the white than in the gray matter as apparently is the paralytic antigen.

Some experiments on allergy in the nervous system have utilized the Arthus phenomenon in which the injection of antigen into sensitized animals intrathecally produced an acute meningitis,^{36,42} or intracerebrally produced a focal hemorrhagic necrosis^{35,43,46,55} and disseminated secondary foci of inflammation and demyelination.⁵¹ Alexander and Campbell⁴⁶ examined the local reaction in guinea pigs and observed a large central zone of hemorrhagic necrosis without patent blood vessels. This was infiltrated with neutrophils, microglia and oligodendroglia and later by astrocytes. It was surrounded by an anemic zone although the blood vessels were patent. They interpreted their findings as demonstrating a primarily vascular hypersensitivity, possibly even primarily endothelial, with secondary thrombosis of vessels. They believed with Gerlach that there was a quantitative difference only between their allergic and control animals; and they disagreed with Rössle, who thought that there were many eosinophiles as well as the quantitative difference. Jervis, Ferraro, Kopeloff and Kopeloff⁵¹ observed not only

a local necrosis typical of an Arthus phenomenon but also scattered cellular reactions with giant cells and demyelination at other points throughout the brain. These, they believed, were indicative of a secondary allergic response, perhaps to the broken-down brain tissue which then became antigenic. These secondary reactions consisted of demyelination, a perivascular inflammatory reaction with giant cells, hemorrhage, thrombosis and fibrosis of blood vessels, necrosis and gliosis.

A type of passive immunization was used by Hurst and Atkinson²⁹ who injected sheep or rabbit anti-pig-brain-serum intrathecally into pigs to produce a widespread meningitis, choroiditis and encephalitis but no demyelination. Hurst²⁹ injected rabbit or goat anti-monkey-brain-serum intrathecally into monkeys with the same results. Jervis⁵⁴ injected Forssman antibodies (rabbit anti-guinea-pig-kidney-serum or anti-sheep-red-blood-cells-serum) into the carotid artery of guinea pigs and observed ataxia and nystagmus. Pathologically, the blood vessels were dilated and congested and there were hemorrhages. There was a diffuse degeneration of neurones and a mild glial reaction; moreover, there were disseminated foci of softening consisting of areas of demyelination with compound granular corpuscles. There were no giant cells and blood cells were thought to be more rare than in the other types of anaphylactic experiments using brain vaccines. Jervis thought that the Forssman antibody passed through an impaired blood-brain barrier. One would expect guinea pig tissue, including brain (although it apparently has not been tested⁵⁷), to contain Forssman antigen with which the injected antibody might react.

Ferraro⁵⁶ discussed the pathology of demyelinating diseases, correlating studies on man and experimental animals, as an allergic reaction of the brain with emphasis on the vascular changes. The vascular reaction consisted of a perivascular exudate which he stated to be always present in acute cases and almost always in chronic cases, which contained lymphocytes and

Gitter cells and other elements, and which itself varied in intensity but was not related to the intensity of the demyelination. The blood vessels were also thickened and frequently thrombosed and there were areas of necrosis and hemorrhages occasionally in the acute cases. Ferraro believed that the term "reactive allergic inflammation" should be added as a new term to explain this vascular reaction. He thought that it coordinated Putnam's views that the thrombi might be allergic or that there might be an allergic instability of the blood-clotting mechanisms which would also produce a vascular type of lesion. He also stated that giant cells up to now had been underemphasized and that these were sometimes glioblastic tumor nodules such as Scherer described. Ferraro thought that the antigen might be derived from an infectious agent, as either an exo- or endo-toxin, or from products of metabolism and diet; that there might be precipitating factors such as fatigue, hyperventilation, trauma, heat, cold or endocrine disturbances; and that later the antigen might be developed from the gray or white matter of the brain. The difficulties in the past, Ferraro believed, have been (1) a tendency to create new clinical or pathologic diseases easily, (2) a lack of discrimination between the chronic and acute pathologic changes, (3) a tendency to be dogmatic in labelling a disease as inflammatory or degenerative and (4) a lack of experimental support for the establishment of a link between the acute and chronic diseases on the basis of a vascular reaction. Parenthetically, we might add that not only do these objections still remain valid, but other objections are at hand, namely, the assumption that processes which look alike pathologically are otherwise alike and the disregarding of important clinical data in the tendency to lump all the demyelinating diseases together. Ferraro believed that hemorrhages and neutrophils were seen only in acute cases and that the processes of edema, lymph stasis, necrosis, lymphocytic, histiocytic and giant-cell reactions and repair were fundamental

to the disease process. He agreed with Klinge that the time-dose relationship was very important, a large dose producing a typical Arthus phenomenon with a hemorrhagic phlegmonous reaction, whereas smaller repeated doses over a period of weeks produced leukocytic and mononuclear inflammation or repeated over several months produced monocytic and histiocytic and giant-cell reaction without neutrophils.

By contrast, Hurst,⁵³ summarizing his experiments on demyelination produced by cyanide, azide or other chemicals, observed that "nevertheless, demyelination must be mediated by enzymatic processes and must ultimately be explained on a biochemical basis." Later, however, in commenting upon his own experiments with cyanide, Hurst²⁹ said: "Massive single or repeated doses usually damaged chiefly the cerebral or cerebellar cortex. Repeated (less often single), rather smaller doses led to bilateral necrosis in the basal ganglia, especially the globus pallidus, or in the cerebral white matter or in both. In a remarkable manner, necrosis often developed suddenly or simultaneously over wide tracts of the white matter after a dose of the poison tolerated previously on many occasions." Again, concerning azide, he stated: "Necrosis in the optic connections followed single or repeated large doses leading to lengthy unconsciousness or developed abruptly from summation of the effects of many small doses each insufficient to evoke marked nervous symptoms. . . . These sudden marked effects could not be explained on the basis of mere accumulation of the poison in the system; it seemed probable that repeated small insults brought the nervous tissues to a state in which a further small dose of the poison, one normally tolerated, produced the most serious consequences." We believe that these statements, especially the last, virtually define the term "hypersensitivity" or "allergy."

SUMMARY

Clinically, allergic manifestations in the nervous system may be produced by the

ingestion of food, inhalation of pollen, injection of serum or vaccination against bacterial or virus diseases or as complications of various diseases. These manifestations include headache, somnolence, convulsions and signs of focal or general central or peripheral nervous system disease. Pathologically, peripheral neuritis, myelitis, meningitis and encephalitis may be found, sometimes with disseminated foci of demyelination or periarthritis nodosa. Whether classical chronic multiple sclerosis falls into this group is not known.

Experimentally, a meningoencephalomyelitis, sometimes with disseminated foci of demyelination, can be produced in ways strongly suggestive that allergy is important: by immunization or vaccination with a presumably normal brain, the antigen apparently being concentrated in the white matter of the central nervous system; by the intracerebral injection of antigen into animals immunized against the antigen, a local hemorrhagic necrosis similar to the Arthus phenomenon also occurring and by the injection of Forssman antibodies into the carotid artery of guinea pigs. Although this condition is comparable to acute disseminated encephalomyelitis or acute multiple sclerosis in human beings, there is no evidence that a picture comparable to classical chronic multiple sclerosis has been reproduced experimentally.

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Normal and Abnormal Heart in the School Child*

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THE value of periodic physical examinations among school children for the purpose of discovering hitherto unrecognized abnormalities of the heart is now well established. However, every examiner should be cautioned that his zeal for uncovering cardiac disease should be somewhat tempered when he must decide upon the significance of adventitious cardiac sounds or cardiac arrhythmias in children. Too often normal variants are erroneously ascribed to structural alterations in the heart or its great vessels. For this reason the present discussion concerning the recognition of the abnormal heart in the school child will be prefaced by allusions to the criteria by which we recognize the normal heart.

THE NORMAL HEART

Functional Systolic Murmurs. 1. *Originating over the Mitral Area:* The systolic murmur heard at the apex of the heart frequently poses a problem of differential diagnosis between an acquired mitral lesion, a congenital defect and a functional murmur. However, if careful attention is paid to the length, intensity, extent of transmission, direction of transmission, point of maximum intensity, constancy of the murmur, associated presence of a thrill or cardiac enlargement, influence of respiration, postural change and exercise, a correct decision as to its real significance can usually be made. The past history, insofar as it may suggest antecedent rheumatic infection, is of great contributory importance. It should be

remembered, however, that about 20 per cent of subjects with unquestionable chronic rheumatic heart disease do not give a history of antecedent rheumatic fever. The quality of the murmur cannot be considered of value in differential diagnosis inasmuch as both functional and organic mitral systolic murmurs can be blowing or harsh. A functional apical murmur, however, never entirely replaces the first heart sound, is rarely loud, is fairly well localized to the mitral area except when it represents a transmitted functional murmur from the pulmonic valve area, is frequently inconstant from day to day or during different cardiac cycles and is considerably modified by postural change, exercise or respiration. In addition, a functional murmur is never associated with a thrill, cardiac enlargement or an apical or basal diastolic murmur.

2. *Originating at the Pulmonic Valve Area:* Functional systolic pulmonic murmurs are extremely common, having been variously estimated to be found in 30 to 60 per cent of healthy children. In contrast to the functional systolic apical murmur, the functional systolic pulmonic murmur is usually harsh and usually replaces the first heart sound. It, too, is never associated with a thrill, cardiac enlargement or a diastolic murmur. It is always accentuated during forced expiration with the child leaning forward. This functional murmur is usually more widely transmitted than the functional apical murmur and, for this reason, can frequently be heard over the apex of the heart and to the right of the sternum. If

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the heart is overactive, a sensation suggesting a thrill may be felt over the site of the pulmonic valve by the palpating hand; with care it easily can be established that the purring quality of a true thrill is lacking. Such a murmur is more frequently encountered in asthenic individuals than in those with other types of body builds. With the aid of the fluoroscope and by comparison between radial and femoral pulses, such functional murmurs can be differentiated from organic, basal systolic murmurs produced by anomalies such as persistent ductus arteriosus or coarctation of the aorta.

3. *Precordial Murmur of Still*: This murmur is similar to the sound produced by the twanging of a tense, low-pitched string of a base violin. The murmur is so low-pitched that it has no blowing quality at all. In fact, its pitch is quite similar to that of the first apical sound itself so that the effect is one of a prolongation of the first sound almost until the second sound is heard, offering difficulty to the examiner in deciding precisely when the first sound really ends. This murmur usually goes unrecognized, probably because of the poor contrast in quality between the first apical sound and the succeeding murmur and because of the relatively few descriptions of it in the literature. The likelihood of its being overlooked is enhanced by the fact that the murmur may be of only moderate intensity, with its point of maximum intensity, usually in the mid-precordium or somewhat below it but sometimes quite near the apex.

Mid-systolic Click. This sound occurs infrequently. It is a definite extracardiac sound but is heard best over the cardiac area, usually being loudest near the apex of the heart. It always appears as though it is very close to the examiner's ear and as though it is immediately beneath the chest piece of the stethoscope. As its name implies, its quality is like that of a click made by the sound device frequently used by elevator starters. It is best heard when the child is leaning forward and usually disappears when the recumbent position is assumed. Its cause is as yet unknown but it is definitely not due to pericardial adhesions or any

other type of structural cardiac disease. It is never associated with cardiac enlargement. It is notoriously inconstant, being present at one examination and absent at another time.

Cardio-respiratory Murmurs. In this category are included all murmurs, systolic or diastolic in time, which are obviously related to the dynamics of respiration. Although the majority are systolic in time, some can be heard during the diastolic phase. They usually sound close to the ear and appear only during the inspiratory or expiratory phase of respiration. Their location is variable although most are heard best over the base of the heart either to the right or left of the sternum. Brief periods of hyperventilation usually abolish these murmurs entirely. They are not associated with thrills or cardiac enlargement. They are extremely inconstant, being heard at one examination and absent at other times.

Split Heart Sounds. In this category are included physiologic split first heart sounds and physiologic split second heart sounds. When physiologic splitting occurs, the two components are not widely separated and there is no associated evidence of heart disease such as the presence of diastolic murmurs or cardiac enlargement. In children, a split second pulmonic sound is a common occurrence.

Physiologic Third Heart Sound. This sound may simulate a gallop rhythm and thereby suggest the presence of organic heart disease. However, the differentiation is easy since the physiologic third heart sound, like all other physiologic heart sounds, is unassociated with enlargement of the heart or significant valvular lesions. Actually, a third heart sound is present during each cardiac cycle in all normal individuals but it is usually inaudible except in those with thin chests and active circulations. The physiologic third heart sound is of low pitch and intensity and is best heard by employing the bell type of stethoscope chest piece lightly applied to the chest wall with the subject in the recumbent or left lateral recumbent position. It practically always disappears when the child is standing. It

occurs at the time of rapid ventricular filling. Its only importance lies in the fact that it may be confused with the summation gallop rhythm of first degree A-V heart block and, therefore, may suggest the existence of an active carditis.

Physiologic Arrhythmias. Exaggerated influence of the vagus nerve upon the heart in children is a usual occurrence. For this reason, sinus arrhythmia or sino-auricular heart block are not uncommon in children. These types of disturbances in rhythm have no pathologic significance and can always be abolished by exercising the child since such a maneuver inhibits vagal activity. They are usually most evident when the child is in the recumbent position and are least evident when the child is standing.

We are now prepared to review the physical findings which indicate or suggest the presence of an abnormal heart in school children.

THE ABNORMAL HEART

Thrills. In addition to detecting the position of the apical impulse, palpation of the heart is important in that it provides us with a means for discovering the presence of thrills. It can be considered an accurate rule that a significant thrill cannot be palpated over the precordium unless there is an audible murmur. For this reason, thrills associated with murmurs which are themselves diagnostic are of relatively little importance. Such a thrill is the apical diastolic or presystolic thrill occurring with the diastolic murmur of mitral stenosis. A continuous, often widespread thrill felt with patent ductus arteriosus gives only confirmatory evidence to the continuous murmur. For this reason, the presence or absence of a thrill does not in any way influence the examiner in deciding whether one is dealing with an abnormal heart. It should be mentioned that the vibration of the contracting ventricle, especially in those with thin chests, may suggest the presence of a thrill but the purring quality of a true thrill is lacking under those circumstances. Statistically, thrills are more often encountered in children in association with congenital

defects; from this standpoint, it is important to seek for thrills in order to help decide whether one is dealing with a congenital or acquired valvular lesion or defects in one of the septa.

Cardiac Enlargement. Of all physical signs, the presence of cardiac enlargement is undoubtedly the most important in detecting the presence of organic cardiac disease. However, in the child in whom structural changes in the heart have occurred either as a result of congenital anomalies or as a result of acquired rheumatic disease, cardiac enlargement will practically never be encountered without associated murmurs which are easily detected. In the child, cardiac enlargement can be established more easily than in the adult because the apex beat is easily palpable. In this regard, it should be remembered that the apex beat in the normal child is felt frequently in the fourth interspace and, therefore, the demonstration of an apical thrust in the fifth interspace should make one suspicious that cardiac enlargement exists. When any pronounced degree of cardiac enlargement exists, systolic retractions are a common occurrence even in the absence of pericardial or pleuropericardial adhesions. When cardiac enlargement and valvular lesions are detected in a colored child, it is most important to palpate for an enlarged spleen because not infrequently such cardiac findings may be the result of sickle-cell anemia. Extreme degrees of cardiac enlargement such as one sees in the adult are practically never encountered in children unless they are confined to bed with some severe, acute cardiotoxic illness. Rarely is it possible to encounter cardiac enlargement in the child in the absence of associated valvular lesions. This type of hypertrophy is the result of so-called idiopathic hypertrophy or the result of glycogen storage disease.

Organic Systolic Murmurs. 1. *Aortic Systolic Murmur:* A systolic murmur heard over the second interspace to the right of the sternum may be accepted as evidence of aortic valve involvement by a rheumatic process. However, there are two exceptions to this conclusion: First, it must be ascertained that

this murmur is not merely transmitted from the pulmonic area. Second, a very soft and labile systolic aortic murmur may be caused by the emotional tachycardia and hypertension of physical examination or by the presence of a secondary anemia. These possibilities can be tested by repeated examination and by obtaining a blood count. Occasionally, such a murmur is found in association with coarctation of the aorta and this diagnosis can be confirmed by noting a disparity between the blood pressure in the arms and the legs or by noting the absence of a pulse over the femoral arteries. Having decided that a systolic murmur in the aortic area is due to *rheumatic involvement of the aortic valve*, the diagnosis of aortic stenosis is still not justified. The latter is rare even in rheumatic hearts which have suffered a series of damaging episodes. The criteria for diagnosing this valvular lesion include a harsh aortic systolic murmur transmitted into the vessels of the neck, low pulse pressure, left ventricular hypertrophy, systolic thrill and absent second aortic sound.

2. *Apical Systolic Murmurs*: If a moderately loud or extremely loud systolic murmur is heard at the apex in the course of a routine examination and is of maximal intensity at that point, is of blowing quality and is transmitted towards the axilla, it is probably well to assume that this murmur is an expression of mitral insufficiency due to rheumatic heart disease. The greatest difficulty in interpreting the significance of an apical systolic murmur arises in the case of the incidental finding of a systolic murmur which is maximal at the apex, is of low or moderate intensity, is of blowing quality and is transmitted very little or not at all to the left. Even if there is no antecedent history of rheumatic fever, it is still not possible to say with assurance that the murmur may not be a residual of rheumatic heart disease since 25 per cent of subjects with chronic rheumatic heart disease are unaware of a previous attack of rheumatic infection. Typical migratory polyarthritides, which is the one sign of rheumatic disease sufficiently dramatic to give rise to a satisfactory de-

scription by the layman, occurs only in a minority of all cases of rheumatic disease in children. Here again, the presence or absence of associated cardiac enlargement may help one decide as to the true significance of a systolic murmur. However, even when all evidences to support the diagnosis of an organic murmur may be lacking, it is still possible that one might be overlooking an organic lesion. Life insurance statistics show that in a random group of individuals with systolic apical murmurs of all sorts there is a mortality rate of 56 per cent above the expected rate. The diagnosis of an organic mitral lesion cannot, therefore, be made solely on the basis of a systolic murmur confined to the apex. *It is recommended* that all such persons be seen periodically at intervals varying up to six months according to the circumstances of the case. Physical examinations at each visit should be supplemented by laboratory, x-ray and electrocardiographic examinations at longer intervals.

Diastolic Murmurs. Provided a diastolic cardiorespiratory murmur can be excluded, the presence of a diastolic murmur always indicates that organic heart disease is present. The two most common diastolic murmurs are those produced by mitral stenosis and aortic insufficiency. Each will now be considered separately.

1. *Diastolic Murmur of Mitral Stenosis*: In attempting to elicit this murmur, the examiner should always place the child in the left lateral decubitus position. In the child, the murmur of mitral stenosis usually does not take the form of the classical crescendo presystolic rumble ending in the snap of the first mitral sound; it appears more frequently as a softer sound, mid-diastolic in time and slightly rumbling in quality which ceases before the first sound appears at the apex. In some children, especially in those who have sustained considerable cardiac damage, it may appear in the classical adult form, namely, the presystolic crescendo rumble ending in the snapping first sound. The diastolic murmur of mitral stenosis in the child may or may not be accompanied by an apical systolic

murmur of mitral insufficiency. Associated enlargement of the cardiac chambers may or may not be evident but usually some cardiac enlargement can be detected. An associated thrill will be palpable if the murmur is sufficiently intense.

2. *Diastolic Murmur of Aortic Insufficiency:* The aortic diastolic murmur is also pathognomonic of an organic valvular lesion, namely, aortic insufficiency. Its presence in the child is practically always the result of rheumatic heart disease and, therefore, is usually associated with a mitral valve lesion. However, there are undoubtedly instances when it can exist as an isolated lesion even when due to rheumatic fever. Rarely is it the result of a congenital anomaly of the aortic cusps, in which case the associated stigmata of coarctation of the aorta are usually present. As in the adult, this murmur frequently escapes detection because it often can be heard only with the child bending forward at an acute angle and with the breath held in expiration. Occasionally, it may be audible only when the child is examined in the prone position. In attempting to elicit this murmur, the examiner should always employ a chest piece with a diaphragm or listen with the bare ear against the chest. In children, the diastolic murmur of aortic insufficiency is likely to appear in somewhat different form than it does in adults. It usually has a very hollow sighing quality as compared with the more low-pitched and full-bodied aortic diastolic murmur of adults. Its point of maximum intensity is usually in the third left inter-space close to the border of the sternum; and its direction of transmission, when it is sufficiently intense, is in a diagonal line toward the apex. However, even when the examiner hears this transmitted murmur first at the apex, its difference in quality from the somewhat rumbling apical diastolic murmur of mitral stenosis should suffice to indicate its origin. An associated systolic aortic murmur is common.

3. *Diastolic Murmur of Persistent Ductus Arteriosus:* A diastolic murmur produced by persistent ductus arteriosus never occurs without a systolic murmur which is best

heard over the pulmonic area. When the diastolic murmur of a persistent ductus arteriosus is present, it lends to the murmur the quality popularly described as "machinery" murmur. Under these circumstances it is practically always associated with a thrill. This is in contrast to the diastolic murmur of aortic insufficiency or the diastolic murmur of mitral stenosis. The diagnosis of persistent ductus arteriosus can also be readily confirmed by a fluoroscopic examination.

Cardiac Arrhythmias. The benign nature of sinus arrhythmia, occasional premature contractions and sino-auricular heart block in children has already been alluded to in an earlier portion of this discussion. However, it should be remembered that occasionally more serious types of arrhythmia may be encountered. For instance, a regular rhythm with a heart rate of 60 or below may indicate the presence of complete A-V heart block. In contrast to a sinus bradycardia, the slow heart rate of complete heart block will not be accelerated by exercise. Also, during some of the cardiac cycles, there usually is a sudden intensification of the first heart sound. In children, complete heart block may be the result of congenital or acquired heart disease. The congenital form is frequently associated with a normal-sized heart and signs of inter-ventricular septal defect but this associated anomaly may be lacking. By contrast, the acquired type of complete heart block is always associated with cardiac enlargement, signs of rheumatic valvular disease, easy fatigability and dyspnea following exertion. Lesser degrees of A-V heart block can be suspected when there is a sudden cessation of all cardiac sounds for the duration of at least one heart cycle or when one can detect summation gallop rhythm. In this type of gallop rhythm, the extra sound is the result of a superimposition of the vibrations produced by auricular systole upon those which occur during the period of ventricular filling. The presence of any degree of A-V heart block in children should always arouse suspicion as to the existence of an active carditis, usually rheumatic in origin.

Juvenile Electrocardiogram

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ALTHOUGH the cause for the phenomenon is not clearly understood, it is a well known fact that the T waves derived from L_{iv} in children are frequently inverted and opposite in direction to those obtained in adults. Recently, however, an examination of the literature failed to reveal a complete description of the juvenile electrocardiographic pattern. Many of the studies on this subject were performed with earlier technics which differed materially from those now employed and resulted in findings not entirely comparable with those obtained at present.

Master, Dack and Jaffe⁸ who studied this problem in 1937, employed seven chest positions beginning at the right sternal border in the fourth or fifth interspace (depending on the age and size of the child) and extending at intervals of 2 cm. to a point 10 cm. to the left of the mid-sternal line. The other electrode was placed on the left leg. With the technic employed the T wave is normally inverted in adults when the exploring electrode is on the left side of the chest. In children they found that the T waves were commonly erect in positions 1, 2 and 3, less frequently in 4 and 5 and generally flat or inverted in 6 and 7. They could find no constant relationship between the degree of axis rotation and the frequency of juvenile configuration of the T waves. The authors ascribed the observed electrocardiographic difference in children to the relative predominance of the right ventricle over the left, as compared to adults and to the comparatively greater A-P diameter of the chest.

At about the same time Messeloff and Pomerantz⁹ made a somewhat similar study of L_{iv} in normal children and ambulatory children with heart disease. They placed the right arm electrode in the fourth interspace just to the left of the sternum and the left arm electrode on the back of the chest at the same level. The authors found such marked and unpredictable variations of T₄ that they concluded that there was "no justification for the routine use of L_{iv} for ambulatory children with heart disease."

On the other hand, Levy and Bruenn⁵ after observing patients with active rheumatic heart disease suggested that T₄ often gave valuable information about the course of the illness. They noted that during a relapse T₄ frequently became more positive. They also put the left arm electrode in the fourth interspace just to the left of the sternum and the right arm electrode posteriorly. Subsequently they employed the left leg as the indifferent point. Their patients were young adults but in view of the frequency of rheumatic fever in youth their reports stimulated further studies in children.

Robinow, Katz and Bohning¹⁰ made an extensive study of the T₄ problem in healthy and rheumatic children. They also investigated the physical and electrical phenomena responsible for the differences noted in the direction of the T waves derived from the chest leads in children and adults. In the technic employed one electrode was placed in the fourth left interspace just beyond the sternum and the other was located posteriorly medial to the right scapula. The

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authors observed a direct correlation between the degree of axis deviation and the direction of the T wave; 80 per cent of the children with right axis deviation had upright T_{4s} while of those without right axis shift only 30 per cent demonstrated the same phenomenon. It was thought to indicate that right axis deviation was an important although not the sole factor responsible for the presence of an upright (juvenile) T_4 in normal children. The shape of the chest was considered to be of greater importance. They also noted that T_4 was not as stable in children as in adults and suggested that this might explain the discrepancies observed between changes in T_4 and the clinical course of the patients. In serial tracings of some twenty normal children they observed that with the passage of time T_4 generally altered toward the adult form but sometimes deviated away from it.

The authors concluded that the practical value of L_{IV} in children suffering from rheumatic heart disease was definitely limited. "Single records in individual cases add no valuable information and serial curves supply data which may be suggestive and are only confirmatory to that obtained from the ordinary standard 3 leads."

Dwan and Shapiro¹ who also studied electrocardiograms in children noted, contrary to the findings of the previous authors, that the four lead tracings in children appeared to be constant from day to day. It was their impression that L_{IV} in children was of distinct value.

Rosenblum and Sampson¹¹ examined the electrocardiograms of fifty children between the ages of one month and sixteen years. Using an earlier technic in which the adult T_4 is normally inverted they found an erect T_4 in 64 per cent of their subjects. Of the remainder, 32 per cent had a diphasic T_4 and 4 per cent had inverted or adult forms.

Heard, Burkley and Schaefer² took electrocardiograms of premature infants and

found erect T_{4s} (juvenile forms) in four of five instances.

Recently, a survey was made of 300 healthy, adult negroes and a significant number of these were found to have what appeared to be a persistence of the juvenile pattern.⁶ The T wave was found to be inverted (present technic, abnormal as made) in CF_2 , CF_3 and CF_4 , sometimes CF_5 and once in CF_6 . The CRT waves, however, were practically always erect, rarely diphasic and never inverted.

In a subsequent investigation⁷ of the electrocardiographic abnormalities found to accompany spontaneous left-sided pneumothorax with mediastinal emphysema, the contour of the T waves derived from the thoracic leads bore a striking resemblance to those seen normally in childhood. The T waves in CF_2 , CF_3 and CF_4 were generally inverted. Here, too, however, the T waves from the corresponding CR leads were erect.

In view of the differences noted between the CFT and CRT waves and since previous electrocardiographic surveys of children did not apparently include chest leads made with the several standard indifferent points, a study of fifty normal children was undertaken.

All of the children selected for this study were between the ages of six and eleven. They were picked at random from the classes of a primary school in grades from one to four, inclusive. The electrocardiograms were made on a wooden table in a room set aside for the purpose at the school. The leads employed were the normal limb leads, CF_2 , CF_3 , CF_4 and CF_5 , CR_2 , CR_3 , CR_4 and CR_5 and CL_2 , CL_3 , CL_4 and CL_5 . The machine used throughout the study was a Sanborn cardiette.

RESULTS

The findings are summarized in Tables I, II, III. Table I is concerned solely with the

TABLE I
RESULTS OBTAINED WITH CF LEADS

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	14	28.0	9	33.3	5	21.7
Inverted or diphasic T_{CF_2} only	18	36.0	9	33.3	9	39.1
Inverted or diphasic T_{CF_2} and T_{CF_3} only	12	24.0	6	22.2	6	26.1
Inverted or diphasic T_{CF_2} , T_{CF_3} and T_{CF_4} only	2	4.0	1	3.7	1	4.3
Inverted or diphasic T_{CF_2} , T_{CF_3} , T_{CF_4} and T_{CF_5}	4	8.0	2	7.4	2	8.7
Totals	50	100.0	27	99.9	23	99.9

TABLE II
RESULTS OBTAINED WITH CR LEADS*

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	47	94.0	24	88.8	23	100.0
Inverted or diphasic T_{CR_2} only	3	6.0	3	11.1	0	00.0
Totals	50	100.0	27	99.9	23	100.0

* Actually there was only one inverted T_{CR_2} . The other two were diphasic. None of the CR leads showed any degree of T wave inversion.

TABLE III
RESULTS OBTAINED WITH CL LEADS

	All Children		Boys		Girls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Purely adult forms	41	82.0	21	77.7	20	87.0
Inverted or diphasic T_{CL_2} only	5	10.0	4	14.8	1	4.3
Inverted or diphasic T_{CL_2} and T_{CL_3} only	3	6.0	2	7.4	1	4.3
Inverted or diphasic T_{CL_2} , T_{CL_3} and T_{CL_4} only	1	2.0	0	0.0	1	4.3
Inverted or diphasic T_{CL_2} , T_{CL_3} , T_{CL_4} and T_{CL_5}	0	0.0	0	0.0	0	0.0
	0	0.0	0	0.0	0	0.0
Totals	50	100.0	27	99.9	23	99.9

results obtained by the use of the CF leads. There were fourteen purely adult forms in the fifty children examined. In the age group studied no constant relationship could be established between the incidence of adult forms and the age of the subjects. Although most of these forms occurred in children of nine, ten and eleven years of age, a large proportion was found in subjects of six, seven and eight years of age. However, a possibly significant difference in the incidence of adult forms was noted between boys and girls; 33.3 per cent of the former and only 21.7 per cent of the latter demonstrated adult graphs. The remainder of the group showed T wave divergence varying between inverted or diphasic T_{CF_2} to inversion of the T wave in all of the CF leads employed. However, it will be noted that the largest proportion of the children had involvement of T_{CF_2} only while progressively smaller groups showed inversion of the T waves in CF_3 , CF_4 and CF_5 .

In no case was there inversion of T_{CF_5} or T_{CF_4} without equivalent or greater involvement of T_{CF_3} and T_{CF_2} . It will be seen from the illustrative tracings that the greatest degree of inversion occurred in T_{CF_2} with progressive diminution in T_{CF_3} , T_{CF_4} and T_{CF_5} or with erection of the T wave at any point after CF_2 . Occasionally there was an abrupt reversal in the direction of the T wave between two consecutive positions of the exploring electrode as in Figure 1.

When the right arm was selected as the indifferent point, a marked change in the incidence of adult forms was noted. Persistence of any trace of T wave negativity was found in only 6 per cent of the fifty children. This took the form of a slight inversion (1 mm.) of T_{CR_2} in one child and a diphasic T wave in the same lead in two others. All of the T waves of these and the other children in leads CR_3 , CR_4 and CR_5 were erect and adult in form.

The tracings resulting with employment

of the CL leads were intermediate between those obtained with the CR and the CF leads. Adult graphs were found in 82 per cent of the children and the number of intermediate forms was proportionately smaller. T_{CL_5} was never negative and T_{CL_4} was inverted in only one instance. In no case were juvenile forms found in the CR or CL leads where the CF leads resulted in an adult pattern.

Two children had unimportant degrees of left axis rotation but no significant right axis deviation was encountered. No correlation could be made in the children studied between the degree of axis rotation and the incidence of adult and juvenile forms.

COMMENTS

It would appear from the findings that the most puerile electrocardiogram is that demonstrating T wave inversion in the CF leads from the left sternal border to or beyond the apex and even into the axilla. Contrariwise, the least juvenile or most nearly adult form is that which shows T wave alteration in the CF_2 position only. It is, therefore, probable that erection of the T wave occurs first in CF_6 or CF_5 and as the child grows older progressively involves CF_4 , CF_3 and finally CF_2 . That this is a steady progress is not, however, definitely known. There is some evidence¹⁰ to indicate that fluctuation of the process may occur in healthy children. This has been observed by the author in several instances.

Of considerable interest and some importance are the results obtained by the use of the CR leads. When the right arm is used as the indifferent electrode, there is little if any apparent difference in the precordial tracings obtained from children as compared to those similarly made on adults. Rarely a diphasic or negative T wave is found normally in adults in the second chest position (CF_2)⁴ and this is perhaps slightly more frequent in younger subjects.

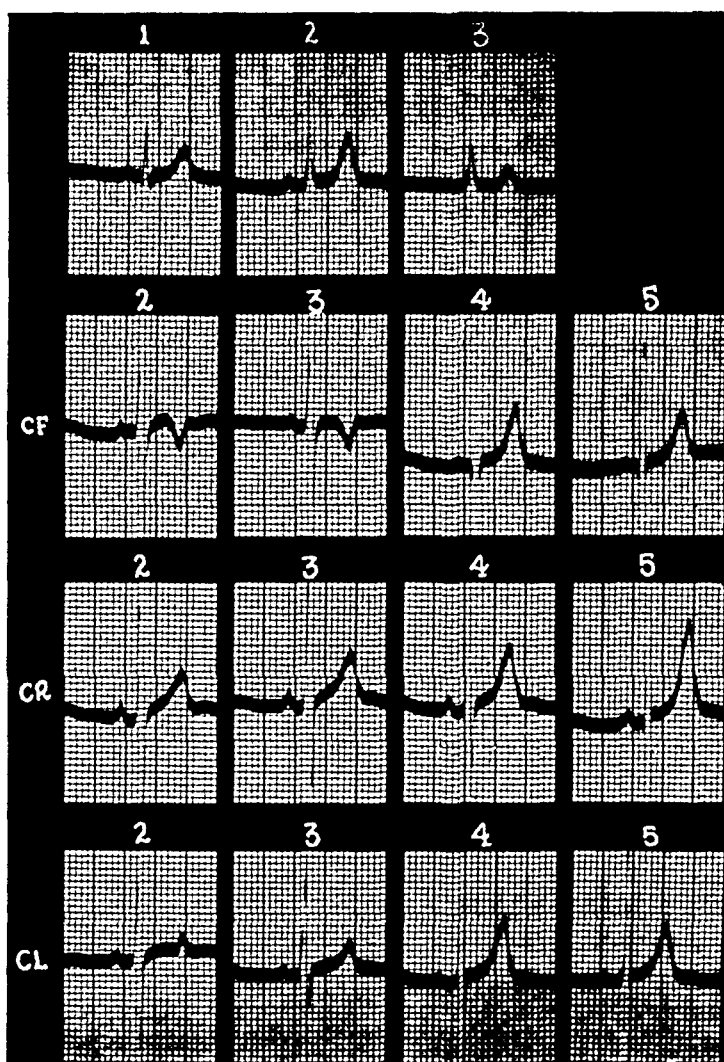


FIG. 1. Characteristic juvenile electrocardiogram demonstrating inverted TCF_2 and TCF_3 with abrupt erection of TCF_4 . T waves in the CR and CL leads are upright.

However, in the more frequently used manner when the exploring electrode was placed just outside the apex no difference at all was found in the CR leads of the fifty children studied. For all purposes, such curves had no earmarks of age and could not be distinguished from an equal number of adult graphs.

Although the study was not repeated, the striking unanimity of direction of the T waves derived from the CR leads in a group as large as this makes it probable that unpredictable variations and fluctuations do not occur. It would appear, therefore, that where the T wave in IVR is of diagnostic

value in the adult it would be of similar importance in the child. It should be of particular interest in following the course of such conditions as rheumatic carditis.

The T waves derived from the CL leads were found to be intermediate between CR and CF. They were neither as positive as the first or as negative as the second. Inverted T waves occurred with sufficient frequency in the CL leads to render them of little diagnostic value.

In considering the causes for the differences noted between juvenile and adult T_4 s Robinow, Katz and Bohning¹⁰ postulated that the shape of the chest and its physical

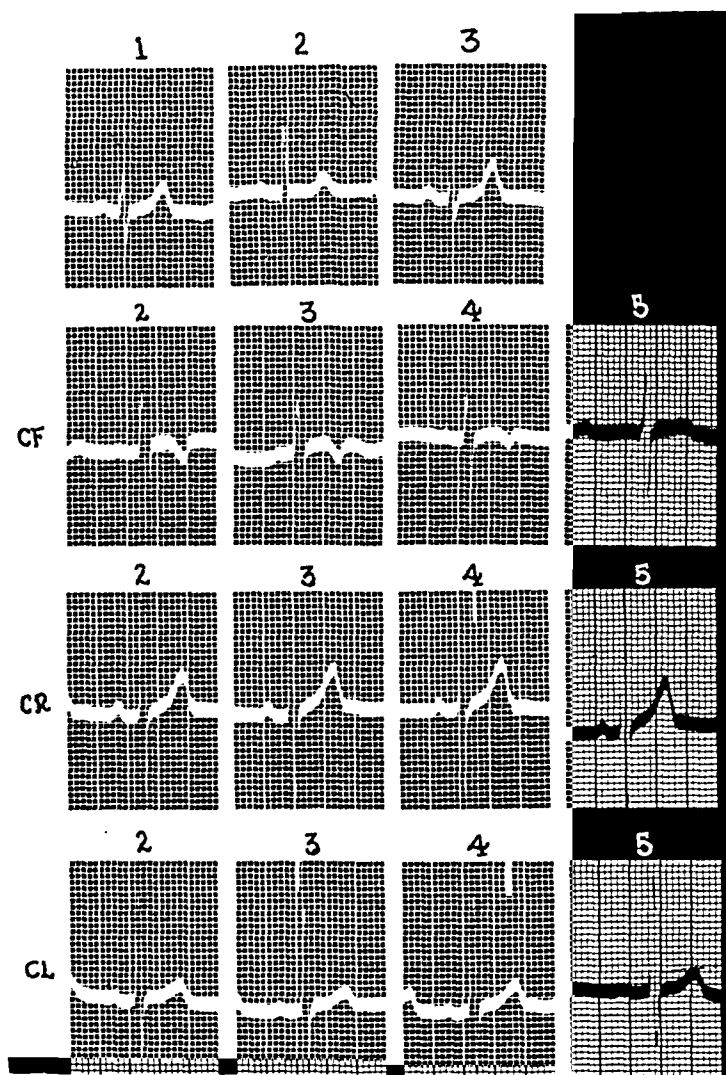


FIG. 2. Characteristic juvenile electrocardiogram with inversion of TCF_2 , TCF_3 and TCF_4 . The T waves in the CR and CL leads are upright.

relation to the heart was of paramount importance. Their work indicated that the amount and character of the tissues interposed between the heart and the chest wall profoundly influenced the character of the electrocardiogram. These features were thought to be sufficiently different in the chests of adults and children to account for the electrocardiographic variations encountered.

In support of this contention are the findings recently observed in two patients with spontaneous left-sided pneumothorax with mediastinal emphysema.⁷ The T waves derived from the CF leads in these patients

showed various degrees of inversion when the patients were in the supine position and the extrapulmonary air was trapped anteriorly. However, when they were erect and the pneumothorax had shifted cephalad the T waves became erect. Although the mediastinal emphysema was in part responsible, apparently in these patients the physical presence of air between the heart and the exploring electrode interfered with the normal surface distribution of the electrocardiac manifestations and resulted in an altered pattern. In spite of this, however, the T waves derived from the CR leads were relatively unchanged. They were somewhat

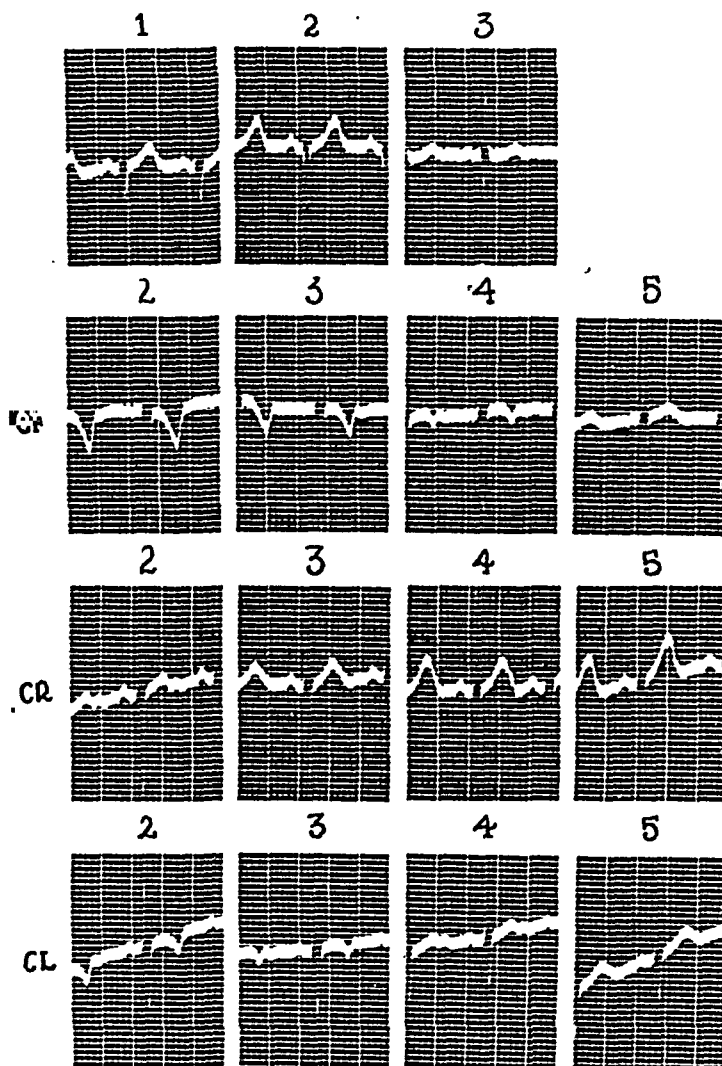


FIG. 3. Characteristic juvenile electrocardiogram. TCF_2 , TCF_3 and TCF_4 are inverted. TCL_2 and TCL_3 are inverted. The T waves in the CR leads are upright.

lower when made in the supine position but were essentially within normal limits. The cause for this is obscure but it appears likely that the electrocardiographic pattern derived from the CR leads is interfered with to a lesser and relatively inconsequential degree by changes in the extracardiac tissues. In a similar manner it is suggested that differences between adult and juvenile chests are of lesser electrocardiographic importance in the CR than in the CF leads.

This, however, should not lessen the value of the CR leads for the diagnosis of purely

cardiac involvement. It is felt that the routine use of IVR in children will be of value and will serve to replace the unpredictable variations and diagnostic inadequacies of lead IVF.

SUMMARY

1. Multiple lead electrocardiograms were made of fifty school children between the ages of six and eleven, in order to determine the normal juvenile electrocardiographic pattern.

2. In the group studied purely adult

forms were more frequently encountered in boys than in girls.

3. Those individuals demonstrating the most juvenile forms had T wave inversions in CF₅, CF₄, CF₃ and CF₂. Those with the most nearly adult forms had negative or diphasic T waves in CF₂ only.

4. It is suggested that change from the puerile to the adult form takes place first in the axillary location and then proceeds medially to the left border of the sternum.

5. The T waves derived from the CR leads of children were not found to be materially different from those of adults.

6. The T waves from the CL leads were intermediate between CR and CF and had no diagnostic advantages over either.

7. No significant relationship could be established between the degree of axis rotation and the incidence of T wave negativity.

8. It is recommended that lead IVR be made routinely in children, in place of IVF which is unpredictable and of little diagnostic value.

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Seminar on Thromboembolism

Dicumarol*

Its Action, Clinical Use and Effectiveness as an Anticoagulant Drug

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THE isolation and synthesis of the compound 3,3'-methylenebis (4-hydroxycoumarin), now generally known as "dicumarol," was reported in 1941 by Link and his associates at the University of Wisconsin.^{1,2} Since that time considerable experience has been accumulated concerning the usefulness of this compound in the prevention of intravascular thrombosis in human beings.

The principal physiologic effect of dicumarol on human beings is the marked inhibition of prothrombin activity as indicated by prolongation of the prothrombin time.^{3,4} This effect is the same as Link and his associates observed in studies on animals. It is generally assumed, although not conclusively proved, that the primary action of dicumarol is a peculiarly selective inhibition of the formation of prothrombin by the liver. This inhibition is temporary and other functions of the liver are apparently not affected even after long continued use of dicumarol. There is evidence that dicumarol has other inhibitory effects on the coagulation mechanism. Spooner and Meyer,⁵ and Wright⁶ have shown that it inhibits adhesiveness of blood platelets and Hurn and her co-workers⁷ have shown that it increases the antithrombic activity of blood serum. It has been shown that when the prothrombin time is greatly prolonged by dicumarol the coagulation time of whole

blood is also prolonged; however, when there is only moderate prolongation of the prothrombin time, the coagulation time of whole blood in glass tubes may not be greatly affected⁴ and cannot be correlated with the prothrombin time. Margulies⁸ has shown that the coagulation time of venous blood drawn into a silicone coated syringe and tested in a silicone coated glass tube at 37°C., is significantly prolonged after dicumarol has been given even when there is only moderate prolongation of the prothrombin time. Dicumarol prolongs clot retraction time. At first we thought that it frequently increased the sedimentation rate of the erythrocytes but subsequent studies have shown that it probably has little if any effect on the sedimentation rate. It has not been shown that dicumarol has any other physiologic effects on the human body except those exerted on the clotting factors of the blood. We have observed four patients in whom minor allergic reactions, urticaria and headache, developed after dicumarol had been administered.

At present, we believe that the only satisfactory and practical method for measuring the effect produced by dicumarol is the Quick prothrombin time test. Other methods for determining the anticoagulant effect of this drug are either difficult, inaccurate or have not been used sufficiently to prove their value. There is some dis-

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agreement as to whether the test is best done on undiluted plasma or diluted plasma. Shapiro and Sherwin⁹ favored the use of a 12.5 per cent solution of plasma in a 0.9 per cent solution of sodium chloride. We still use only undiluted plasma because we believe that the end points are more definite and consistent when undiluted plasma is used.

Dicumarol is effective when administered orally. This is a relative advantage from the standpoint of simplicity of administration. No satisfactory preparation for parenteral administration has been developed. This is a disadvantage from the standpoint of accuracy of dosage. The effect of dicumarol is delayed for twelve to seventy-two hours or longer after a dose has been given. This is a distinct disadvantage when a rapid anticoagulant effect is desired. The effect of dicumarol may persist for seventy-two hours or longer once it has developed. This may be an advantage in maintaining the anticoagulant effect but is a disadvantage when it is desirable to stop the anticoagulant effect rapidly, for example, in case of bleeding.

Early in our experience with dicumarol, it was found that prolongation of prothrombin time varied greatly among different patients after the administration of a certain amount of dicumarol and that the degree of response was usually unpredictable. Hepatic insufficiency, renal insufficiency and dietary insufficiency were found to augment the effect greatly. Some diseases of the gastrointestinal tract, recent operations on the stomach or the intestine and repeated vomiting may greatly decrease or nullify the effect. In patients in whom thrombosis occurred recently they are frequently but not always more resistant to dicumarol; however, there undoubtedly are other factors which may produce relative sensitivity or resistance to the drug which are entirely unpredictable and which unfortunately

may vary somewhat from time to time in the same patient. For these reasons the production and maintenance of a certain degree of prothrombin deficiency by dicumarol becomes an individual problem in each case. The amount of dicumarol administered on each day may be arbitrarily fixed but the days on which the drug is given have to be selected on the basis of daily prothrombin time tests. We have believed that it is simpler and just as satisfactory to give one daily dose as it is to give the same amount in divided doses. If daily prothrombin time tests are not done, it is always uncertain whether the doses of dicumarol are producing the desired effect, an inadequate effect or an excessive and possibly dangerous effect.

Because of the importance of the Quick prothrombin time test as a guide to effective and safe administration of dicumarol, it is necessary to emphasize some of the technical features of this test which apparently are not generally appreciated. The exact mechanics of performing the test are simple¹⁰ but the variable in the test is the potency of the thromboplastin. It is useless to state that the normal prothrombin time, as indicated by this test, is a certain number of seconds and it is equally useless to state that a certain degree of prothrombin deficiency, for example 20 per cent prothrombin, is indicated by a certain number of seconds, because the times for these concentrations of prothrombin are entirely dependent on the particular thromboplastin which is used and the way in which it is prepared.¹¹ Thromboplastins from the same source prepared in the same way also may vary in potency. For these reasons it is necessary at all times for the laboratory worker to know the percentages of prothrombin indicated by prothrombin times of any number of seconds. It is also advisable that the laboratory worker report the prothrombin time to the clinician in terms of per cent of

the normal concentration of prothrombin rather than in seconds. If clinicians become accustomed to discussing concentrations of prothrombin in terms of percentages rather than time, it is possible to compare the results of the tests performed in many institutions or by individual physicians in different laboratories. If seconds are used no such comparison is possible. Some misunderstandings have arisen in the computations of prothrombin percentages from prothrombin times in seconds. There is no way that percentages of prothrombin can be computed accurately by any linear relationship between an elevated prothrombin time and a normal prothrombin time. The only accurate way to compute prothrombin percentages from prothrombin time is to compare frequently the values obtained for prothrombin deficient plasma with values obtained with the same thromboplastin for serial dilutions of two or three samples of normal plasma. Dilutions are theoretically best made with prothrombin-free plasma but actually the same results may be obtained by diluting with an 0.9 per cent solution of sodium chloride. For example, the prothrombin time of normal plasma and of 10, 20 and 30 per cent solutions of normal plasma in 0.9 per cent solution of sodium chloride are obtained with the particular thromboplastin in use. A comparison of the prothrombin time of the plasma of the patient receiving dicumarol with the prothrombin times for these diluted samples of normal plasma will permit a reasonably accurate report in terms of percentage of normal prothrombin. It is worthy of note that the relatively great decrease of prothrombin from 100 to 50 per cent of normal is indicated by only a slight increase in the prothrombin time while the relatively slight decrease in the concentration of prothrombin from 10 per cent of normal to 5 per cent of normal is indicated by a relatively great increase in the prothrombin time.

Our experience has led us to believe that when dicumarol is used as an anticoagulant it is advisable to keep the concentration of prothrombin between 10 and 30 per cent of normal as calculated by the previously mentioned method, because we have encountered thrombosis in some patients in whom the concentration of prothrombin was greater than 30 per cent and most of the instances of major bleeding have occurred when the concentration of prothrombin was less than 10 per cent of normal. When the concentration of prothrombin was kept between 10 and 30 per cent of normal few instances of major bleeding and almost no instances of thrombosis have occurred. This zone of effectiveness and relative safety is a comparatively narrow one and some observers have been satisfied with less drastic reduction in the concentration of prothrombin. This may be sufficient to prevent thrombosis in some patients but is certainly less effective if the stimulus to thrombus formation is strong. We believe that if dicumarol is used at all, a strong attempt should be made to secure the optimal effect in each patient.

The plan of dosage which we have continued to employ since our early experiences with the drug is quite simple. The entire amount for one day is given in a single dose: 300 mg. of dicumarol are given on the first day and 200 mg. are given on each subsequent day that the concentration of prothrombin is greater than 20 per cent of normal. On days when the concentration of prothrombin is less than 20 per cent of normal no dicumarol is given. Even with this method the variability of response among different patients is considerable. In the majority of patients it is quite easy to maintain the concentration of prothrombin between 10 and 30 per cent of normal but in some patients who are sensitive the concentration of prothrombin may quickly drop below 10 per cent of normal. In these

patients we usually cut the dose from 200 to 100 mg. In an occasional patient who is very resistant we increase the dose from 200 to 300 mg.

It has been shown that in most patients large doses of menadione bisulfite (synthetic vitamin K) given intravenously, usually within a few hours will increase prothrombin percentages which have been lowered excessively by dicumarol.¹² This is particularly true in patients who are found to be hypersensitive to the drug when it is employed in the usual doses as indicated previously. If the concentration of prothrombin drops below 10 per cent of normal and remains there for two successive days, 30 mg. of menadione bisulfite may be given intravenously and this usually will raise the concentration of prothrombin above 10 per cent.

We have given dicumarol to hospital patients for periods as long as nine months and have maintained an optimal effect on the basis of daily prothrombin time tests. In a few patients who were not in the hospital, attempts were made to continue dicumarol therapy for even longer periods with less frequent checks of the concentration of prothrombin and to regulate the dosage on the basis of a pattern which has been found effective for the individual patient after a few weeks of carefully controlled therapy. We do not recommend this inadequately controlled therapy since we believe that it cannot be considered either persistently effective or safe.

The use of dicumarol with concurrent heparinization for the first few days is the best method for rapidly instituting and maintaining anticoagulant therapy. Since heparin acts rapidly, it is used to secure an anticoagulant effect during the period after administration of dicumarol has begun and before an adequate effect of the dicumarol has developed. During this period it is usually sufficient to give 50 mg. of heparin

intravenously every four hours until the concentration of prothrombin is less than 20 per cent of normal as a result of the effect of dicumarol. Blood for the prothrombin time tests should be withdrawn at least three and a half hours after a dose of heparin has been given as heparin also increases the prothrombin time.¹³

In previous publications we have listed certain contraindications to administration of dicumarol; namely, hepatic insufficiency, renal insufficiency, purpura of any type, blood dyscrasias with bleeding tendency, particularly thrombocytopenia, and subacute bacterial endocarditis. We have believed that the use of any anticoagulant is contraindicated after recent operations on the brain or spinal cord, not because the danger of bleeding is greater but because the consequence of even a minor degree of bleeding at the operative site is great.

Extra caution and an appreciation of increased risk of bleeding are advisable when dicumarol is administered to patients who have open ulcers, granulating wounds or drainage tubes. Nutritional deficiency may increase sensitivity to dicumarol.

The risk of bleeding during administration of dicumarol is small if the plan of dosage described previously is followed and if the contraindications and cautions are observed. Minor bleeding, such as transient epistaxis, local ecchymoses in the skin, small hematomas in operative wounds and microscopic hematuria can be disregarded. Serious and prolonged bleeding has been noted from operative wounds, ulcerating lesions of the gastrointestinal tract and from the urinary tract. It has been encountered by us postoperatively in only 1 per cent of patients who have had thrombosis and in only 2.5 per cent of those who have not had thrombosis prior to administration of dicumarol. We have encountered serious bleeding in 1.4 per cent of non-surgical patients. We have seen widespread hemor-

rhage and ecchymosis in only one patient, a patient with subacute bacterial endocarditis and renal insufficiency, two conditions which are now considered contraindications to the use of dicumarol. The patient died as the result of hemorrhage. We have seen three patients who have died as the result of bleeding from the gastrointestinal tract after they had received dicumarol. One of the patients died before much prothrombin deficiency had developed and the other died after the prothrombin time had returned to normal and had remained normal for several days; therefore, it is unlikely that dicumarol was a factor in the production of the fatal hemorrhage in either patient. The third patient had an inoperable carcinoma of the stomach and the hemorrhage occurred during moderately severe prothrombin deficiency produced by dicumarol.

If serious bleeding occurs it is our practice to give 60 mg. of menadione bisulfite intravenously each day until bleeding stops. Usually it stops within twelve hours after the first injection. We also transfuse 500 cc. of freshly citrated blood if much blood has been lost and repeat this as frequently as necessary. The transfusion of blood is done largely to replace blood. It supplies some prothrombin also but the effect of this usually is transitory.

The purpose of giving dicumarol is to prevent thrombosis. As far as is known it has no effect on a thrombus that has already occurred or an embolus that has already lodged in an artery. Thus the use of dicumarol is always prophylactic and not curative. It is given to patients who are known to have or have had thrombosis, in order to prevent extension of thrombosis or thrombosis in other vessels. Naturally it is not certain that further thrombosis will develop if the patient is not treated. The rationale for the use of dicumarol, therefore, depends to some extent on the percentage chance of thrombosis developing within the

period during which dicumarol can be given with adequate supervision. In some situations the percentage chance of further thrombosis or embolism is fairly well indicated by statistical studies of large numbers of cases.

The rationale for the use of dicumarol for the prevention of pulmonary embolism in a patient with venous thrombosis or thrombophlebitis is based on the concept that only a freshly formed thrombus will become detached and form an embolus. If the thrombus remains in the vein for more than a few hours it rarely if ever becomes detached. Thus, in a patient with clinically recognizable venous thrombosis or thrombophlebitis, if extension of thrombosis or fresh thrombosis in other veins can be prevented, embolism can be prevented. Actually, in a large series of patients with postoperative thrombophlebitis who have been given dicumarol, fatal embolism has not occurred although the expected incidence of fatal embolism among such patients is approximately 6 per cent. This strengthens the concept that an embolus only develops from a newly formed thrombus, since the only effect of the dicumarol in such patients is the prevention of fresh thrombosis.

Our greatest experience with dicumarol has been in the prevention and treatment of postoperative thromboembolic disease and this has been the subject of several reports.^{4,14,15,16} To date we have supervised the postoperative administration of dicumarol to 1,983 patients; 352 of these patients were given dicumarol because of clinically evident thrombophlebitis and 329 because of pulmonary embolism or pulmonary infarction. As compared with a large series of similar cases in which anticoagulants had not been given, the incidence of subsequent thromboembolic episodes was reduced from 43.8 to 1.0 per cent and the incidence of fatal embolism was reduced from 18.3 to 0.3 per cent among the patients with

embolism; the incidence of subsequent thrombotic episodes was reduced from 25.3 to 2.8 per cent and that of fatal embolism was reduced from 5.7 per cent to zero among patients who had thrombophlebitis. Preliminary heparinization was employed in some patients in both groups. In addition, we have given dicumarol postoperatively to more than 1,302 patients for prophylaxis against thrombosis and embolism. Of these patients, 143 had had thrombosis or embolism at some time prior to the immediate operation. No pulmonary embolism developed in any of these 1,302 patients and thrombosis developed in only two. This was localized to small veins in both subjects. After operation we have continued the administration of dicumarol until the patients have been ambulatory for several days and until they left the hospital; the period of administration usually lasted seven to twenty days. Patients were not kept in bed or in the hospital longer than usual because they were receiving dicumarol.

Dicumarol has been administered successfully to patients with postpartum thrombophlebitis and pulmonary embolism for the purpose of preventing subsequent thromboembolic episodes.¹⁷ Our experience with the administration of dicumarol for this purpose has been limited to nineteen cases (four patients with pulmonary embolism and fifteen with thrombophlebitis). In none of these patients did further thrombosis or embolism develop and in none was there abnormal bleeding or increase in the lochia. Treatment was begun as early as the fifth postpartum day. Two mothers were nursing their babies, and repeated studies of the prothrombin time of the infants showed values which were normal even though the concentration of prothrombin among the mothers was between 10 and 30 per cent of normal. Experimental studies have shown that when relatively large doses of dicumarol are given to lactating rats the

nursing baby rats may bleed and die;¹⁸ however, the doses of dicumarol given to the mother rats were relatively much greater than the doses which are given to human beings, in fact, they were sufficient to produce generalized bleeding and death in the mother rats as well. This situation cannot be compared to the controlled administration of therapeutic doses of dicumarol to human beings.

We have given dicumarol to 182 patients with thromboembolic disease which occurred as a complication of trauma, infectious diseases, congestive heart failure, carcinoma, blood dyscrasias or varicose veins or which was of the idiopathic type. Of these patients, 138 had acute thrombophlebitis and forty-four recently had had pulmonary embolism. During treatment with dicumarol fatal embolism did not develop. Non-fatal embolism developed in three patients and subsequent venous thrombosis occurred in four patients. This series of cases is rather small and we have no statistical data to indicate the expected incidence of thrombosis and embolism during the period of treatment if anticoagulants had not been given; however, it is our impression that the incidence was markedly reduced by dicumarol. In several of the patients there had been repeated thromboembolic episodes before dicumarol was given but these ceased after dicumarol was administered. It is not possible to state how long dicumarol should be given to such patients, particularly in those patients in whom thrombophlebitis or embolism complicates congestive heart failure or carcinoma or in patients with recurrent idiopathic thrombophlebitis. It is recognized that in these patients a tendency to thrombosis may exist for a long time, during which it is unpractical to give dicumarol continuously.

We have given dicumarol to seventy-six patients with chronic occlusive arterial disease of the extremities, in some instances

for periods as long as four to six months. In forty patients the disease (thromboangiitis obliterans or arteriosclerosis obliterans) was considered to be in the active phase when dicumarol was given. In thirty-six patients it was given for prophylaxis after amputation. In none of these patients was there any evidence of recurrence or extension of arterial or venous thrombosis during the period in which dicumarol was given. We do not believe that it is practical to give dicumarol to patients with chronic occlusive arterial disease of the extremities unless the disease is in an active phase or unless amputation is necessary.

In patients with acute arterial occlusion of the extremities, either by arterial embolism or thrombosis *in situ*, we have used dicumarol, always with preliminary heparinization, for the purpose of preventing further intracardiac and peripheral arterial thrombosis.¹⁹ It has been our experience that secondary and distally propagating thrombosis from the site of the occlusion frequently occurs in these patients after the arterial spasm has relaxed and that this secondary thrombosis is often the factor which precipitates gangrene. To prevent this secondary thrombosis it is necessary that anticoagulant therapy be started as early as possible and certainly within twenty-four hours after the arterial occlusion has taken place. We have treated eleven patients with arterial embolism and sixteen patients with acute arterial thrombosis *in situ* with heparin and dicumarol. In all of these subjects the diagnosis was made early and the administration of the anticoagulants was started within twenty-four hours after the occurrence of the embolism or thrombosis. There was survival of the extremity in ten of the eleven patients with arterial embolism and in thirteen of the sixteen patients with acute arterial thrombosis. We believe that anticoagulants plus procedures to eliminate

arterial spasm and avoidance of thermal trauma to the affected limb are important in the emergency treatment of acute arterial occlusion of the extremities.

There have been four reports of the treatment of acute myocardial infarction with dicumarol. The rationale has been to prevent further episodes of coronary thrombosis during the period of healing of the infarction and to prevent intracardiac thrombosis, venous thrombosis, pulmonary embolism and thrombosis in peripheral and cerebral arteries, all of which have been known to be relatively frequent complications of acute myocardial infarction. Nichol and Page²⁰ reported the treatment of forty-four patients who had a total of fifty instances of myocardial infarction. These authors expressed the opinion that the incidence of secondary thromboembolic complications was significantly reduced. Peters, Guyther and Brambel²¹ compared the results obtained in fifty cases of acute myocardial infarction in which the patients were treated with dicumarol with the results obtained in sixty similar cases in which dicumarol was not administered. They found that the dicumarol apparently reduced the mortality rate from 20 to 4 per cent and that the incidence of pulmonary embolism was reduced from 16.6 to 2 per cent. Wright²² administered dicumarol to seventy-six patients with myocardial infarction. In thirty-three of these patients the disease was uncomplicated but in forty-three of the patients the drug was given after repeated episodes of coronary occlusion or thromboembolism had occurred. Four patients in the first group and eleven patients in the second group died. The author believed that this represented a reduction in mortality for the types of patients treated. In a recent article, Parker and Barker²³ compared the results obtained in fifty cases of acute myocardial infarction in whom dicumarol was administered with the results

obtained in one hundred similar cases in which this drug was not administered and which previously had been reported by Nay and Barnes.²⁴ Secondary thromboembolic complications occurred in 4 per cent of the patients to whom dicumarol was administered and in 37 per cent of the patients to whom this drug was not administered. The mortality rate was 10 per cent in the cases in which dicumarol was administered and 13 per cent in the other group of cases.

In each of these four reports on the treatment of acute myocardial infarction, the series of cases in which dicumarol was administered is too small to permit conclusions as to the value of this drug; however, when considered in the aggregate they appear to indicate that such treatment is of value in preventing secondary thromboembolic complications and probably in the prevention of further myocardial infarction. Further observations on larger series of cases from several institutions will probably be available in the near future.

If anticoagulants are to be used in the treatment of acute myocardial infarction, it would appear that the administration of dicumarol and preliminary heparinization should be started as soon as the diagnosis is made and that the administration of dicumarol should be continued for at least four weeks.

SUMMARY

Dicumarol is a potent and valuable anti-coagulant drug. When used properly it appears to prevent intravascular thrombosis in almost all patients. There is considerable and unpredictable variation in sensitivity to dicumarol among different patients. Dosage of dicumarol must be guided by the effect produced in each patient as indicated by the degree and duration of prothrombin deficiency which develops and is indicated by determinations of the concentration of

prothrombin in the blood. It is unwise to use dicumarol unless adequate facilities for determining the prothrombin time are available. If the prothrombin is kept between 10 and 30 per cent of normal by administration of dicumarol, thrombosis will almost certainly be prevented and serious bleeding is very unlikely to occur. The action of dicumarol is delayed. When a rapid anticoagulant effect is desired concurrent heparinization is necessary for the first few days. We have found that dicumarol has prevented fatal pulmonary embolism and recurrence or extension of venous thrombosis in patients who have had postoperative nonfatal pulmonary embolism or thrombophlebitis. There is some incomplete evidence to the effect that it will prevent peripheral thrombosis, pulmonary embolism and further coronary thrombosis in patients who have had acute myocardial infarction. Dicumarol with preliminary heparinization is valuable in the treatment of acute arterial occlusion of the extremities. It has also been used safely in patients in whom thrombophlebitis and pulmonary embolism complicated the puerperium and various diseases, in patients with idiopathic recurrent thrombophlebitis and in those with chronic occlusive arterial disease. While statistical confirmation is lacking, it is our impression that in many of these patients thrombosis and embolism have been prevented by administration of dicumarol.

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Dissecting Aortic Aneurysm^{*}

An Unusual Case Having a Previous Healed Dissection and Later Slow Dissection of All Major Aortic Branches

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EVER since Shennan's able monograph in 1934, dissecting aortic aneurysm has received increased attention as evidenced by the number of reports appearing in the literature. It is the purpose of this paper to report an additional case followed both before and after the accident in some detail, which was remarkable because there was a healed dissection, and because the pathological course could be traced clinically from beginning to exitus along the entire aorta and its branches.

Although dissecting aortic aneurysm has been recognized by the pathologists for over two hundred years, the first description having been made in 1728, it was not recognized clinically until 1856. Between that first recognition and 1933, only five correct ante-mortem diagnoses were reported, but in the last ten years it has been described some fifty times. The symptomatology is now sufficiently well defined so that it should usually be diagnosed before death.

PATHOGENESIS

Dissecting aneurysm is a lesion produced by penetration of the circulating blood into the substance of the wall of a vessel with subsequent extension of the effused blood for varying distances between its coats. The sac communicates with the original lumen through a rupture or ruptures of the inner layers of the wall and then usually breaks

through either to the exterior or back into the lumen. The primary rupture is usually transverse to the long axis of the vessel while the second tear is along the longitudinal axis. It occurs more often in males with a ratio of two to one, and usually in the fifth to seventh decades. Hypertension is almost always present; syphilis of the aorta is rarely present, and if present is associated with the atherosclerosis responsible for the dissecting aneurysm.

The primary rupture most often occurs in the arch of the aorta in the region of the ductus arteriosus and the right pulmonic artery and is, as stated, transverse. The secondary rupture is usually central to this near the reflexion of the pericardium, and more often into the pericardium than elsewhere, but may be at any level. The dissected space may therefore extend centrally into the coronary arteries or distally to the termination of the iliac arteries. Any vessel arising from the aorta may be dissected and its branches involved.

It is generally conceded that the cause of the primary rupture is the diastolic thrust where the blood comes back against the suddenly closed aortic cusps, especially where the heart is heavy and supported in part by the aorta. This is especially true when the aorta has been stretched by a short, strong ductus arteriosus or compressed by the right pulmonic artery as it passes

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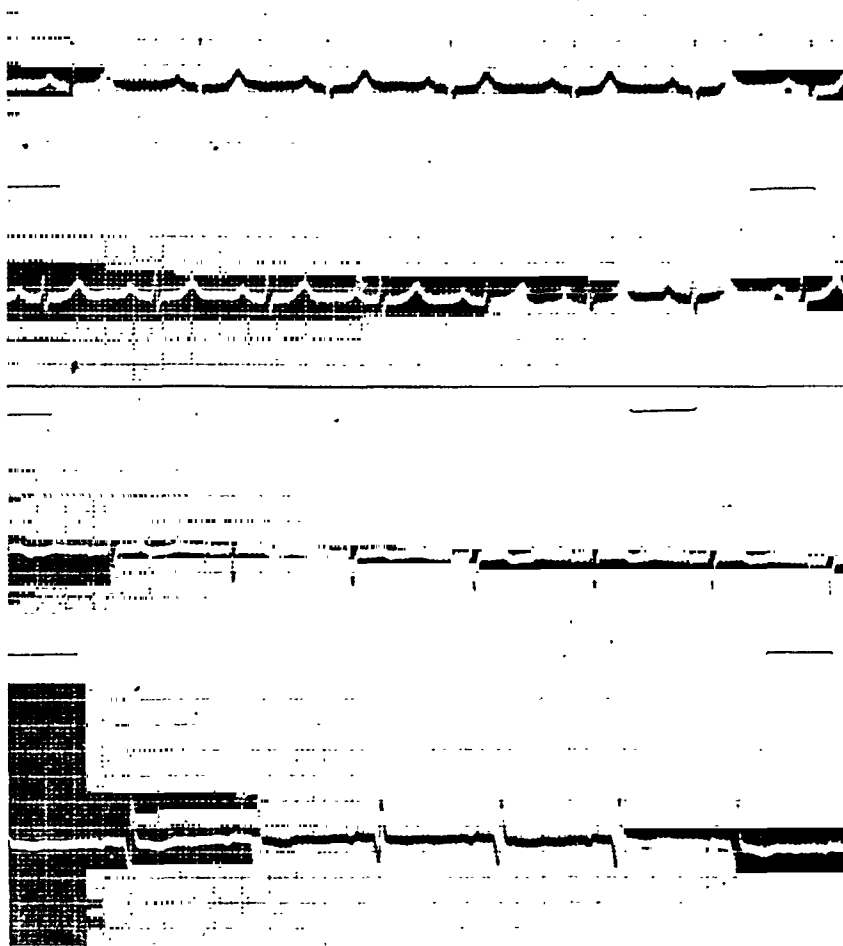


FIG. 1. Electrocardiogram taken at time of original small dissection misdiagnosed as coronary occlusion.

under the arch. However, ruptures do not usually occur through atheromatous plaques but at their edges or through an apparently intact intima. It is therefore believed that degenerative changes in the media which extend into the intima predispose to this condition. And especially does this medial degeneration predispose to dissection between strong inner and outer coats rather than to rupture directly through the whole aorta at once. The pathogenesis includes many factors, mainly: (1) A rise in blood pressure following external or internal trauma; (2) primary rupture through the intima; (3) dissection between the coats and (4) rupture of the sac to the exterior or re-entrance into the original lumen.

By external trauma is meant any sudden

jarring; by internal trauma any unusual and especially sudden exertion.

SYMPTOMS

Symptoms of Primary Dissection. It is characterized by a sudden onset without premonitory symptoms in a patient otherwise in good health except for hypertension. There is a feeling of something going wrong, often not clearly defined, and usually in the thorax.

Pain is almost invariable and maybe in the thorax, abdomen or both, and very often in the back. This may be extremely severe. Characteristically, the pain usually travels downward from its point of onset, taking from a few minutes to several days. Collapse often occurs. Other symptoms de-

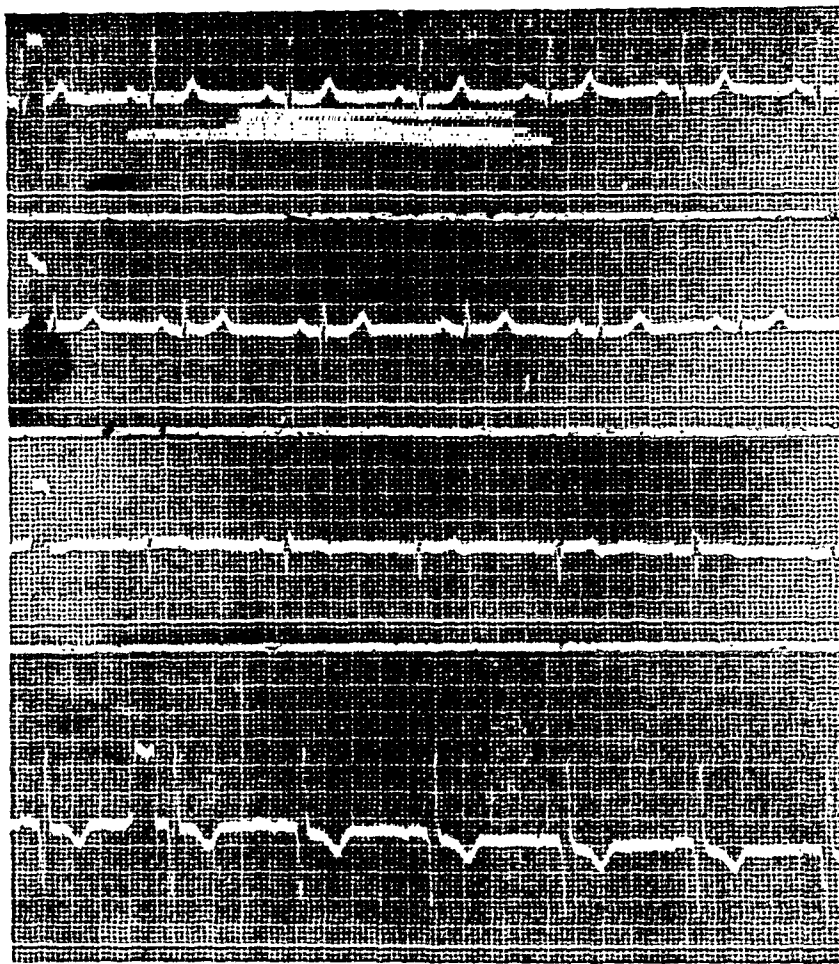


FIG. 2. Electrocardiogram at time of second dissection. Note change in T_3 and T_4 .

pend on the rapidity of dissection and the vessels involved. These include choking or strangling sensations in the chest, cyanosis or swelling of the face and neck, dyspnea or orthopnea, dysphagia, pain in the abdomen, kidney regions or legs, and in our case, uncontrollable hiccough and jaundice. The pulse and blood pressure are usually unchanged. There may be slight fever, and leucocytosis is often present. There is usually no change in the electrocardiogram unless dissection extends to the coronary arteries. There is often characteristic widening of the entire aortic shadow to left and right.

DIFFERENTIAL DIAGNOSIS

In the absence of correct diagnosis of dissecting aneurysm various other diagnoses

are often entertained and vary with the rapidity and extent of the dissection. These include, coronary or mesenteric obstruction, pulmonary embolism, rupture of the heart, gastric crisis, renal or pancreatic colic, or perforated abdominal viscus.

The course of the disease is variable, but unless re-entrance into the original lumen occurs, practically always results fatally. Exitus may occur from a minute to several months after the original tear, and death is almost always by perforation and without warning. Terminal perforation occurs most often into the pericardium, and then into the left lung or pleura, the free mediastinum or the abdomen.

There is no treatment except such symptomatic help as can be given and which may prolong life a few weeks or months.



FIG. 3. Chest x-ray showing typical barrel-shaped aortic shadow with shadow of aneurysm extending through stomach air bubble.

CASE REPORT

This case shows the usual history of long-standing hypertension with enlarged heart. There was a beginning dissecting aneurysm two years earlier having some features of coronary occlusion and diagnosed as such in spite of a normal electrocardiogram.

He later suffered from a typical dissecting aneurysm in which the flow of blood in the dissected media could be traced clinically through its entire extent and then lived four months to die suddenly from rupture of the aneurysm into the left pleura and lung.

This male patient, age fifty-two, was first seen December 6, 1935, complaining of occipital headaches for six months. He had been under a severe nervous strain and worry for five years and had worked long hours.

Physical examination showed him to be markedly overweight, of ruddy florid complexion. The peripheral arteries felt somewhat sclerotic, and the heart was slightly enlarged to the left. All other physical findings, including ophthalmoscopic examination, were normal. The blood pressure was 230/130 in both arms taken while he was sitting up. The urine was

normal except for many hyaline casts. The blood count was normal.

He was sent to the Presbyterian Hospital where renal function tests were normal, and blood chemistry was normal except for slightly elevated total non-protein nitrogen and uric acid. An electrocardiogram and x-ray film of the chest showed nothing but left axis deviation and slight enlargement of the left ventricle. He was kept in bed for several days. With sedatives and rest, his blood pressure dropped rapidly to 150/110. He was advised to shorten his hours of work, reduce his weight, avoid excitement, and was given small doses of phenobarbital and potassium iodide. The headaches disappeared, and the weight was reduced thirty pounds. The blood pressure averaged 150/116 for the next year. Beginning in January, 1937, he increased his hours of work and stopped his medicine, but continued relatively free from headaches until March, 1937.

First Small Perforation. While walking to the office after a heavy breakfast he was seized with a severe pain beneath the sternum, the pain being described as a pressure. He was taken home and seen an hour later. The pain was agonizing, requiring morphine, the pressure was 126/92, the pulse 112 with a regular rhythm, but the heart tones were indistinct and of tic-tac quality. There was no radiation to arms, neck or back. The patient was seen with Dr. James B. Herrick, who found dullness to the left of the spine from the fourth to the ninth thoracic vertebrae, and agreed that the probable diagnosis was a coronary thrombosis, in view of the history of pain, drop in blood pressure, and tachycardia. He was kept quiet for six weeks, then allowed a gradual increase of physical activity so that at the end of four months he was walking five miles daily; by this time the pressure had risen to about 180/100. The heart findings were again normal, and electrocardiograms taken every six months subsequently showed no remarkable change from the original tracing taken before the accident. (Fig. 1.)

His condition remained the same during the next two years except that he had two attacks of renal colic in April and November, 1938. He was seen every six months during that period for electrocardiogram and renal function tests.

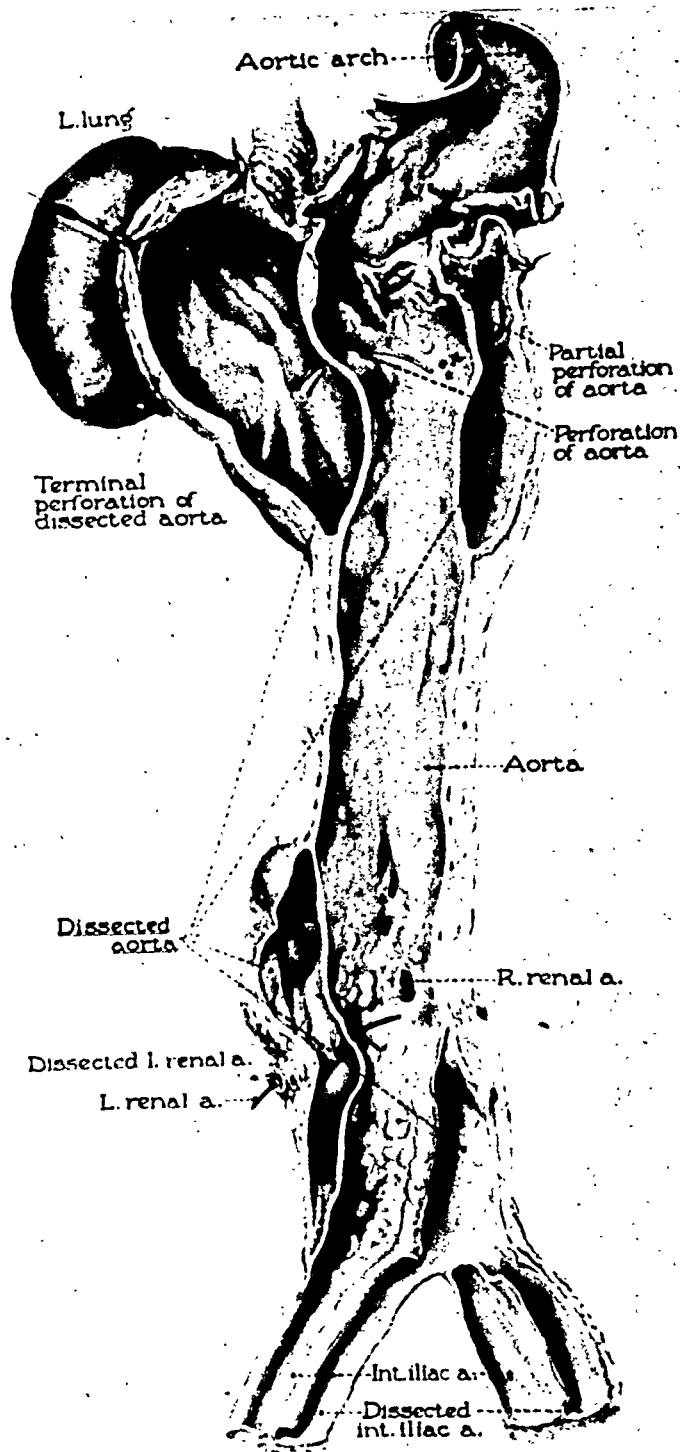


FIG. 4. Diagram drawing showing original healed partial perforation; second perforation which led to dissection; dissected aorta and its branches and terminal rupture of dissected aorta.

All of these were normal during this period except for the persistent hypertension of about 190/115, and a slight elevation of the uric acid and non-protein nitrogen content of the blood.

Onset of Second Dissection. On January 4,

1939, he was awakened at 1 A.M. with very severe pain beneath the mid-sternum going through to the back at the level of the angles of the scapulae directly in the mid line. Sometimes it would be worse in front and sometimes worse



5

FIG. 5. Photograph taken at autopsy showing the aorta to be composed of a tube within a tube.



6

FIG. 6. Root of aorta showing atherosclerosis; perforation through intima and its relation to aortic valve.

in the back. The pain was at all times excruciating, causing him to groan, to toss in bed and walk the floor. Sometimes it seemed to be pulsating or wave-like but did not subside at any time. He drank whiskey and hot water, and induced vomiting without relief. A physician was called and gave him a hypodermic of gr. $\frac{1}{4}$ of morphine at 3 A.M., 4 A.M. and 5 A.M. without the slightest relief, and then ordered four one quart enemas of soap suds and turpentine, all with no relief. He described the pain as entirely different in character and location from that experienced three years before, and from that of the attacks of renal colic in the past.

When seen by us at 3 P.M. he was groaning and writhing in pain. Temperature, pulse and respirations were normal. The trunk was warm, the extremities cold and clammy. The blood pressure was 230/116 in both arms. Examination was entirely normal except for slight cardiac enlargement to left and right, unchanged from previous examinations. There was also slight dullness in the back from the third to the sixth

vertebrae on the left near the spine. By this time he stated that the substernal pain had lessened and the back pain was one or two inches lower.

He was brought to the Presbyterian Hospital in an ambulance with an admission diagnosis of dissecting aneurysm. The following additional findings were: red count and hemoglobin normal but the white blood count was 16,000. Urine was entirely normal. The cardiogram was unchanged from previous tracings except for slight inversion of T_3 and T_4 . (Fig. 2.) A flat plate of the abdomen was normal. The blood pressure was 180/108.

He was seen by Dr. Herrick at 8 P.M. who confirmed the above and suggested a chest fluoroscopy and x-ray. These showed a pulsating area behind the heart extending from the aortic arch to about one inch above the diaphragm which pushed the lower esophagus forward and to the left.

Progress of Dissection. His clinical course was extremely stormy. The temperature rose rapidly

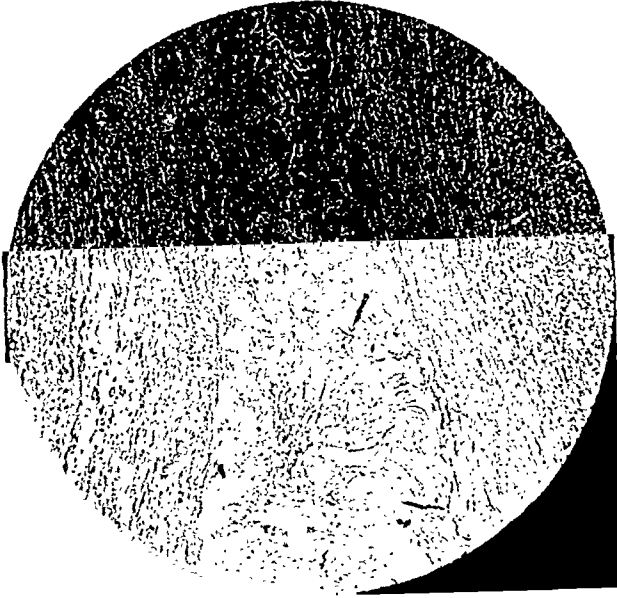


FIG. 7. Fatty medial plaque replacing muscle tissue.



FIG. 8. Earlier original dissection into medial plaque with replacement by fibrous tissue and endothelialization of intima.

to between 101 and 103°F., where it remained until January 15th, the eleventh day of the disease. The pulse ranged from 100 to 120, and the respirations between 22 and 32 per minute. The blood pressure, however, remained elevated, at no time falling below 184 systolic and 96 diastolic. The pain was excruciating, neces-

sitating very frequent injections of pantopon, an average of twelve injections daily for twelve days. In addition he was given large doses of bromide by rectum and by mouth.

At eleven o'clock the first night he began to hiccough. This continued with only brief remission for seven days in spite of everything that

could be done. On January 5th, an x-ray plate of the chest and abdomen showed a shadow extending through the diaphragm about half way through the stomach air bubble, suggesting, with the hiccough, that the aneurysm had become lower, being at about the level of the first and second lumbar vertebrae. (Fig. 3.) On January 6th and 7th the sclerae became yellow and the urine gave a positive test for bile. On the morning of the 7th he complained of pain in the epigastrium and that afternoon, pain in the region of the left kidney, the latter feeling "like the old kidney stones" except that it did not radiate downward to the groin and testis. This left lumbar pain recurred frequently during the next three days, (probably the time of the left renal artery dissection). By January 16th the abdominal pain had traveled down to the area between the navel and the symphysis pubis, and occasionally the feet were very cold. On January 24th it was noted in the record, "the last two days it has seemed possible to feel a slightly tender mass whose outline is very indefinite just to the left of the midline midway between navel and pubis. No definite pulsation is felt, but one wonders whether the dissection has extended to the bifurcation of the aorta."

By January 25th, the twenty-first day, the temperature and respiration had become normal and all pain had disappeared. By the first of February the pulse was in the seventies and remained so until February 11th, the thirty-ninth day in the hospital, when he returned to his home. He remained quiet there for ten days and then went to Florida, it being felt that since the prognosis was most grave, he would be happier there. His physical activity was greatly limited, but he took short automobile rides and was contented and entirely free of symptoms.

Final Rupture into Pericardium. On April 29th, 115 days after the original accident, after eating a large dinner, he rose from the table, walked about ten steps, clutched his chest, regurgitated a little bright red blood, and died within a minute of the onset of pain. The autopsy was done by Dr. Robinson, of Fort Lauderdale, and the heart and aorta sent to Chicago for further examination. (Fig. 4.)

The essential findings in the autopsy as performed by Dr. Robinson, "The heart was of

normal size. The ascending and transverse arch of the aorta was moderately dilated as were the great vessels arising from the arch, to a less degree. Just distal to the left subclavian artery the antero-medial surface of the aorta was adherent to the pleura of the left upper lobe of the lung. In this area there was a tear in the wall of the aorta, measuring about 5 mm. in diameter. The tear was irregular in outline, and no evidence of clot formation was present on the margins. The aortic wall at this point was less than 1 mm. in thickness and was deep purplish red in color over an area of 2 cm. in diameter. The ecchymotic area was very friable. There was also a slit 2 cm. wide and 1.5 cm. deep in the arch of the aorta completely endothelialized. On opening the abdominal aorta it was found that the aorta consisted of a tube within a tube. (Fig. 5.) The external tube had a wall consisting of fibrous tissue and was approximately 2 mm. in thickness. The internal surface of the outer tube and the external surface of the inner tube were covered with a smooth shining surface. In several places there were antemortem thrombi adherent to the inner surface of the external tube. The inner tube was the aorta, and the two tubes were in contact and their walls merged over only a narrow area. The circumference of the aorta and its caliber were diminished by about 30 per cent. (Fig. 6.) The endocardial surface of the aorta showed a moderate atherosclerosis. The above condition extended as far distally as was dissected, that is, into the internal and external iliac arteries.

The posterior surface of the left upper lobe of the lungs were adherent to the aorta at the site of the rupture. The apex of the left upper lobe was firm, non-crepitant and deep purplish red in color. This area cut with increased resistance and the cut surface bled fully. The remainder of the lungs were normal."

Microscopic examination of the tissues was done by Dr. Apfelbach at the Presbyterian Hospital.

Microscopic sections of the aorta revealed multiple medial plaques in which the muscle was replaced with fat, often somewhat caseous, and fibrous tissue. The earlier beginning dissection was seen to have healed over with fibrous

tissue. The wall being lined with regenerated endothelium. (Figs. 7 and 8.)

The coronary arteries and the myocardium were normal.

COMMENTS

A case of dissecting aortic aneurysm has been presented in which it was possible to trace the dissection through the various

branches of the aorta. This patient had had an earlier beginning dissection which at the time was thought to be a somewhat unusual coronary occlusion.

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Acute Thrombocytopenic Purpura Complicating Rubella*

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THROMBOCYTOPENIC purpura is an unusual, but not rare, complication of many acute infections;^{8,10,13,14,15} however, it has seldom been described as being associated with rubella. In the past few years interest in German measles has been stimulated by the high incidence in the armed forces and because of the large epidemic in Australia.

During the winter season of 1945 to 1946, at the Regional Station Hospital, Fort Bragg, North Carolina, we have observed two cases of thrombocytopenic purpura associated with rubella which are worthy of report in order to emphasize the occurrence of this complication. The blood picture of a small group of eleven consecutive patients with this disease has been studied in order to determine if there is a depression of platelets in the peripheral blood of these patients and the findings are recorded and discussed.

CASE REPORTS

CASE 1. A twenty-two year old, white soldier (W. B.) was admitted on February 6, 1946, because of fever, slight malaise and a rash on his face, neck and body of eight hours' duration. There were no symptoms of an acute upper respiratory infection. No drugs had been taken.

The physical examination on admission revealed a soldier in no acute distress with a temperature of 100.2°F., a pulse rate of 100 per minute, respiratory rate of 22 per minute. There was a fine, pink maculopapular rash over the face, neck and trunk. Marked occipital and postauricular lymphadenopathy was present.

There were no Koplik spots seen. The laboratory studies of the peripheral blood and urine were within normal limits.

No drugs were administered. The rash began to fade rapidly and the temperature returned to normal the day following admission. On February 8th, the rash had entirely disappeared and the patient was asymptomatic. A spontaneous epistaxis occurred on the evening of February 9th, and it was found to be very difficult to stop by the usual methods. The following day bleeding from the nose recurred and at that time many purpuric lesions averaging 2 to 3 mm. were seen over the entire body and extremities. Further examination revealed spongy, bleeding gums. A tourniquet test was markedly positive. Laboratory investigation showed the platelet count to be 4,000 per cu. mm.; red blood count of 4,800,000 per cu. mm.; a hemoglobin of 90 per cent (Newcomer) and a normal white blood cell count and differential. In determining the bleeding time it became necessary to apply pressure over the puncture wound after thirty minutes, due to the profuse bleeding; oozing from this wound still occurred twenty-four hours later. The clotting time was four and one-half minutes and the venous blood clot did not retract at all in twenty-four hours. The prothrombin time was normal.

A blood transfusion of 500 cc. of fresh, whole blood was given without reaction. There was no elevation of the blood platelets noted following this transfusion. Large doses of vitamin C were given parenterally each day.

The patient continued to have marked bleeding from his gums as well as severe nose bleeds which were not successfully controlled by nasal packs with ephedrine. Hemostatic globulin was used on nasal packs commencing February 12th,

* From The Medical Service, Regional Station Hospital, Fort Bragg, N. C.

with apparent benefit. There were no further nose bleeds but minimal bleeding from the gums continued until February 14th, at which time the mucous membranes began to appear healthier. A blood transfusion of 500 cc. was given on February 17th because of the patient's anemia and clinical weakness. The patient

minute and the respirations were 20 per minute. A generalized, red, morbilliform rash was noted on the face and body. The posterior cervical and occipital lymph nodes were markedly enlarged. Koplik spots were not present. The laboratory studies of the peripheral blood and the urine were normal on admission.

TABLE I
LABORATORY DETERMINATIONS IN TWO CASES OF THROMBOCYTOPENIA PURPURA

Case	Date	Platelets per Cu. Mm.	Bleeding Time	Clotting Time	Red Blood Cells	Hemoglobin (Newcomer) Per Cent	Tourniquet Test
I	February 10	4,000	30 minutes*	4½ minutes	4,800,000	90	++++
	February 11	14,000	4,300,000	90	
	February 12	18,000	3,950,000	80	++++
	February 13	10,000	3,850,000	80	
	February 14	21,000	2,820,000	51	
	February 15	13,000	3,500,000	59	
	February 16	86,000	3,900,000	70	++
	February 19	132,000	12 minutes	4½ minutes	4,260,000	80	
	February 20	122,000					
	February 21	118,000	3,920,000	80	
	February 23	120,000	4,650,000	90	
	February 25	132,000	4,820,000	95	
	March 4	184,000	4,480,000	90	
	March 8	290,000	3½ minutes	4 minutes	4,570,000	95	Negative
II	March 25	80,000	11 minutes	4½ minutes	4,560,000	90	++
	March 26	126,000					
	March 27	127,000	4,180,000	80	
	March 30	210,000	4 minutes	4½ minutes	4,840,000	90	Negative

* Pressure applied after thirty minutes due to profuse bleeding. Oozing from puncture wound still taking place twenty-four hours later.

gradually improved; the purpura had entirely disappeared by February 20th, and the gums appeared normal at that time also. The soldier was returned to full duty on March 11th. The laboratory findings were normal on discharge. (Table I.)

CASE II. This eighteen year old, white soldier (H. O.), was admitted to the communicable disease ward of The Regional Station Hospital on March 23, 1946, complaining of fever, malaise and a rash over his face and body of twenty-four hours' duration. There were no symptoms of an acute respiratory infection. No drugs had been taken.

The physical examination at that time revealed a well developed, well nourished, white male who did not appear to be acutely ill. The temperature was 102.8°F., pulse was 92 per

The patient rapidly became asymptomatic and his rash began to fade on the second hospital day. No drugs were administered. Three days following admission many small purpuric lesions averaging 1 mm. in diameter were noted over his entire body. At this time, he was found to have a markedly positive tourniquet test, a platelet count of 80,000 per cu. mm., bleeding time of 11 minutes, clotting time of 4½ minutes and poor clot retraction at 24 hours. The patient showed no evidence of spongy gums, epistaxis or other bleeding tendencies. At this time he was afebrile and the temperature did not become elevated during the remainder of his hospital stay. The following day the platelet count was 26,000 per cu. mm.; the daily changes are noted in Table I. By March 29th, the purpuric rash had faded markedly and only minute

areas of pigmentation remained. On March 31st, the patient showed no further evidence of a rash, he was asymptomatic and returned to full duty on the following day.

PLATELET COUNTS IN ROUTINE CASES OF RUBELLA

Material. Eleven consecutive patients with rubella were carefully studied by means of platelet counts, red blood cell and white blood cell determinations and tourniquet tests. Bleeding and clotting times were performed on patients having lowered platelet counts.

Methods. Platelet counts were done by the direct Thorndike method. The bleeding time was determined by means of the Duke method and the coagulation time by the use of glass capillary tubes. The tourniquet tests were performed by counting the number of petechiae in an area 2.5 cm. square and 4 cm. below the antecubital fossa after leaving the blood pressure cuff inflated for fifteen minutes mid-way between the patients' systolic and diastolic blood pressures. Normally no more than ten spots should appear five minutes after the pressure is released.

Results. In three instances the number of platelets in the peripheral blood was definitely diminished and in one (Case III) the diminution was marked. (Table II.) This patient also showed a markedly positive tourniquet test, this being the only one positive in the entire series. The bleeding time in this patient was 6 minutes and the clotting time $2\frac{1}{4}$ minutes when the thrombocytes were at the lowest point. After the number of platelets had returned to normal the tourniquet test was negative and the bleeding time was $3\frac{1}{2}$ minutes.

COMMENTS

Dunlap in 1871,³ described a case of purpura associated with German measles. This was soon followed by similar reports by Cheadle,² Erskine⁴ and Glaister.⁵ These

authors all described instances of purpura having its onset soon after the fading of the rubella rash, but the description of the laboratory findings was meager. Pitten¹³ and Gunn⁶ each reported an instance of rubella complicated by thrombocytopenic

TABLE II
PLATELET COUNTS AND TOURNIQUET TESTS ON ELEVEN
CONSECUTIVE CASES OF RUBELLA

Case	Platelet Counts			Tourniquet Test on Admission
	Admission	Third Hospital Day	Sixth Hospital Day	
I	278,000	249,000	250,000	Negative
II	250,000	272,000	Negative
III	88,000	204,000	250,000	Markedly positive
IV	198,000	260,000	250,000	Negative
V	334,000	300,000	Negative
VI	123,000	193,000	Negative
VII	311,000	302,000	Negative
VIII	265,000	248,000	250,000	Negative
IX	311,000	320,000	309,000	Negative
X	131,000	220,000	Negative
XI	351,000	307,000	301,000	Negative

purpura of a mild degree, manifesting the typical blood findings of thrombocytopenia, prolonged bleeding time, normal clotting time and diminished clot retraction. Warren et al.,¹⁷ reported two cases demonstrating both renal and intestinal bleeding, in addition to purpura, epistaxis and gingival bleeding.

Thrombocytopenic purpura has been associated with measles more commonly than with rubella^{8,10,14,16} and similarly with many other acute infections, such as varicella,¹⁵ infectious mononucleosis,^{7,14} acute upper respiratory infections,⁸ lobar pneumonia⁸ and acute sinusitis.⁸

Olef⁹ has demonstrated by a careful study that thrombocytopenia may occur during the initial stage of many acute infections. It therefore seems reasonably clear that the thrombocytopenia occasionally associated with rubella may be regarded as an example of this non-specific reaction.

The exact mechanism of the occurrence of this phenomenon is unknown but it is believed to take place in one of several ways. Olef⁹ attributed the thrombocytopenia in acute infections to the clumping of the platelets around the invading organisms as a means of overcoming infection by the body. McLean et al.,⁸ reported purpura occurring six to nineteen days after the onset of the acute infection and suggest the possibility that the thrombocytopenia may be an allergic manifestation particularly affecting the megakaryocytes in the bone marrow. Patek¹⁰ likewise is of the opinion that the decreased number of platelets in the peripheral blood may be the result of an allergic or hypersensitive state. The production of thrombocytopenia in acute infections may be a manifestation secondary to increased capillary permeability in which the platelets are diminished in number, helping to reinforce the weakened vessel walls.^{10, 11, 16}

It seems reasonable to assume that the thrombocytopenia may be brought about by a direct depression of platelet formation in the bone marrow by the infectious agent, the megakaryocytes being normal in number.¹⁶ Purpura may then occur due to a combination of the lack of platelets to plug defects in the walls of injured capillaries and the increased bleeding time.

The treatment of thrombocytopenic purpura complicating an acute infection should be one of conservatism. Complete bed rest is essential. Measures should be taken to stop bleeding from the nose. Hemostatic globulin used on nasal packs appeared to be effective in stopping the epistaxis in Case 1. Bleeding gums will rarely be of sufficient severity to cause great concern. Hemorrhage from the urinary or gastrointestinal tract is much more difficult to manage and usually all efforts are useless until a spontaneous remission occurs. Transfusions are of value if the blood loss is sufficient to necessitate them; they are of no value in either increas-

ing the platelet count or diminishing the bleeding time. Ascorbic acid may be of value because of the increased capillary fragility, but there is no evidence to make one believe that vitamin K is beneficial. Splenectomy is unnecessary in most instances and it is doubtful if such a procedure is ever justified in thrombocytopenic purpura resulting as a complication of an acute infection. This operation, at least, should certainly be reserved for those patients having fulminating, uncontrollable hemorrhages.

SUMMARY

1. Two cases of thrombocytopenic purpura complicating rubella are reported. In Case 1 the purpura was noted the third day after the onset of the illness and about thirty-six hours after the disappearance of the rash of German measles. In Case 2 the purpura appeared on the fourth day of illness and at a time when the primary rash had almost completely disappeared.

2. Platelet counts and tourniquet tests were performed on eleven consecutive patients with rubella, three of whom revealed an initial lowering of the platelets. One of these patients had a moderate thrombocytopenia, a markedly positive tourniquet test and a prolonged bleeding time.

3. The theoretical mechanisms of this phenomenon were discussed.

4. The treatment of thrombocytopenic purpura complicating acute infections should be directed toward controlling the hemorrhages and treating the resulting anemia. Recovery occurs spontaneously within a few days in most instances, and splenectomy is probably never necessary.

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Fulminating Meningococcemia with Gangrene*

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SINCE the publication of Herrick's classical report,¹ an increasing amount of attention has been paid to the bacteremic features of infection with *Neisseria intracellularis*.² It is now generally believed that in 10 to 35 per cent of systemic invasions by this organism, the meninges are not involved at the time the initial diagnosis is made. The higher incidence of bacteremia without meningitis probably represents only the fact that in more cases the diagnosis is being made earlier. Acute, subacute or chronic forms of meningococcic septicemia have been described, ranging in severity from a mild and relatively innocuous disease to a fulminating and highly fatal one. The latter type, often referred to as the Waterhouse-Friderichsen syndrome, is usually so rapidly fatal that relatively few clinically demonstrable complications have been recorded. However, with the advent of such specific therapeutic agents as the sulfonamide drugs and penicillin, more patients are surviving, even though they may have had infections of an extremely malignant type. Consequently, some cardiovascular complications are being observed.

It is the purpose of this paper to report a case of fulminating meningococcemia with gangrene of the lower extremities. This complication appears to be something of a rarity; at least, it is not described in recent reports³⁻⁶ of large groups of cases recorded from army training camps. Herrick men-

tioned one case, but did not give any details; Bernstein⁷ reported a case of meningococcic meningitis with peripheral gangrene, and Hayes and Whalen⁸ also reported a case in which most of the characteristics of the Waterhouse-Friderichsen syndrome were presented, with bilateral gangrene of the toes and multiple zones of cutaneous gangrene. Their patient recovered, as did Bernstein's and ours, after treatment with penicillin and sulfonamide drugs.

CASE REPORT

An eighteen year old seaman was admitted to a naval hospital on November 13, 1945, in a disoriented condition, with a temperature of 100°F. (37.7°C.). On admission, he complained principally of chills, sore throat, headache, and extremely painful legs and toes. He had suddenly been prostrated by a severe chill the evening before while at work, and at that time had noticed severe pain in his feet. Results of physical examination were essentially negative, except for extensive purpuric and ecchymotic lesions over the dorsa of his hands and over the dorsal and plantar surfaces of both feet; a few scattered purpura were seen on other areas of his body. The feet were cold, blue and hypersensitive, and there was unmistakable evidence of interference with arterial circulation. There was neither evidence of meningeal irritation nor signs of shock or vascular collapse; the blood pressure remained consistently within normal limits.

A diagnosis of acute meningococcemia was made. The patient was immediately given an initial dose of 4 Gm. of sulfadiazine; thereafter,

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he received 1 Gm. every four hours. Subsequently, a dose of 30,000 units of penicillin was ordered to be administered intramuscularly every two hours.*

Lumbar puncture revealed that the cerebrospinal fluid was clear and colorless and that the pressure was 240 mm. of water. The number of cells and protein content were normal. Leukocytes numbered 28,000 per cu. mm. of blood. The erythrocyte count and results of the Kahn test were normal. The sedimentation rate of erythrocytes was 30 mm. in one hour (modified Cutler method). Culture of material from the throat produced *Neisseria intracellularis*. Culture of specimens of blood and material from blebs produced the same organism, type II A. The organism exhibited complete sensitivity to 0.5 units of penicillin per cc. of culture medium. Results of laboratory procedures including the prothrombin time, bleeding time, clotting time, icterus index, determination of blood urea nitrogen, and urinalysis were all within the range of normal. A roentgenogram of the thorax showed no abnormalities.

The subsequent clinical course of this patient, although generally satisfactory, revealed that the infection was somewhat refractory to treatment. The patient continued to have daily elevations of temperature, in spite of the use of increased doses of penicillin administered intravenously and continued sulfadiazine therapy. The administration of sulfadiazine was temporarily discontinued on the sixth hospital day in the belief that it might have been the cause of the continued pyrexia. The administration of penicillin was continued in the interval. This procedure proved to have no effect on the temperature curve. On November 16th (three days after admission of this patient), results of a routine electrocardiogram were within normal limits and those of examination of the heart were objectively negative. Three days later, gallop rhythm developed, and a blowing systolic

murmur was heard at the apex cordis, with decreased intensity of both the first and second sounds. At the base, the murmur was greatly diminished in intensity and the pulmonic second sound was accentuated. This was tentatively interpreted as evidence of acute myocarditis and possibly of acute endocarditis. Results of the electrocardiogram remained normal, however, and by November 20th the gallop rhythm had disappeared and the systolic murmur was greatly diminished in intensity. Between November 26th and December 2nd, the patient was afebrile. On November 30th, the use of all specific medications was discontinued. On December 2nd, the fever returned and on December 6th, the temperature reached 102°F. (38.8°C.). The administration of both penicillin and sulfadiazine was resumed and the patient became afebrile on December 10th. Results of culture of specimens of blood were negative during this episode, and no new purpuric lesions appeared.

The circulation of the patient's feet continued to show evidence of inadequacy, which seemed to increase rather than decrease. Moderate edema developed in both feet, and the ecchymotic lesions of the feet and toes persisted. Pulsations of the posterior tibial arteries remained normal, but pulsations of the dorsalis pedis artery could not be felt in either foot. No new areas of ecchymosis appeared, but edema, bluish discoloration and coldness persisted and a red line of demarcation gradually made its appearance. (Fig. 1.) At no time was there objective evidence of peripheral neuritis or of caudal myelitis, conditions which have been described as complications of meningococcal infections. By November 21, 1945, the distal portion of the right great toe and the great second and third toes on the left foot had become definitely gangrenous. Block of the periarterial sympathetic fibers with procaine hydrochloride was attempted at one time, in the hope that this would arrest the gangrenous process, but the procedure proved to be of no avail. The gangrenous parts were kept at complete rest under a heat cradle, with frequent changes of warm moist antiseptic packs. Although low-grade fever persisted, with occasional increases in temperature after December 10th, the general condition of the patient gradually improved. On December 19, 1945, all

* Since this article was submitted for publication we have found three additional references to patients with meningococcemia and gangrene, one in 1917 and two recent ones in 1946 and 1947. In the two latter subjects there was extensive gangrene requiring amputation of the lower extremities. One patient required skin grafting for areas of cutaneous gangrene while the other lost portions of his fingers. This brings the total number of such patients now on record to seven. References are appended on the bibliography (12, 13 and 14).



FIG. 1. A, appearance of patient's ankles; B, plantar surfaces during the third week of illness, showing gangrene and ecchymotic regions. (Official United States Navy drawing, courtesy United States Naval Hospital, Oakland, California.)

gangrenous toes were removed surgically. The patient improved rapidly thereafter and, after plastic repair of the distal portions of the feet, he was dismissed in good general health, with only minor impairment of his gait.

COMMENT

Although acute meningococcemia frequently may be explosive in onset, at times it is characterized by a paucity of symptoms and a relatively mild course unless meningeal involvement occurs. An erythematous or purpuric rash, myalgia, arthralgia, fever and chilling usually are present, and there may also be nausea and vomiting, headache and sore throat. The spleen is sometimes palpable. In many cases a subacute form of the disease superficially resembles acute rheumatic fever. When the disease is milder, the prognosis is not unfavorable, barring the appearance of endocarditis or meningitis. In some cases recovery without medication has occurred; three such cases in which the patients were children have been reported by Silverthorne.⁹

It is of interest that in Bernstein's case, in Hayes and Whalen's case, and in the case we have reported, evidence of definite vascular occlusion involving the toes ap-

peared within the first twenty-four hours after the onset of symptoms. Our patient complained of cold, painful feet and toes as an initial symptom, and although the pain subsequently diminished, the interference with circulation persisted and was of sufficient magnitude to lead to gangrene. In Bernstein's case, causalgia involving one arm was a prominent and prolonged feature; but arterial involvement of the arm was not noticed.

Although the cause of gangrene in meningococcic septicemia has not been definitely established, Bernstein has postulated that it is a trophic disturbance based on a common, widespread, vascular lesion, embolic or autochthonous, or on a peripheral vasospasm caused by a toxin produced by the invading organism. It is not difficult to believe that the symmetric lesions in our case could have been caused by bacterial emboli involving the distal distribution of the dorsalis pedis arteries.

In our case, there was no good reason to consider the possibility of an associated endocarditis. Although meningococcic myocarditis, associated with endocarditis, has been recorded in a small number of cases,¹⁰

a search of the literature reveals only seventeen cases of meningococcic endocarditis and twelve of myocardial involvement, usually with fatal termination. Holman and Angevine⁴ recently have reported two such cases of myocarditis; in one the myocarditis was proved at necropsy and in the other it was disclosed by serial electrocardiograms. In our case, myocarditis and bacterial endocarditis were at one time suspected, although never definitely proved. Once treatment had been instituted, results of all subsequent cultures of specimens of blood were negative, and signs and symptoms referable to the heart rapidly disappeared.

Among the three types of *Neisseria intracellularis*, types I, II and II A, there has been reported no appreciable variance of virulence; there has been, however, evidence that strains of type II may be found more commonly in the presence of endemic meningococcic septicemia, whereas strains of type I predominate during epidemics of the disease (Thomas).³ At times, no organism can be demonstrated during life, even when fulminating meningococcemia is present. Martland,¹¹ in a series of nineteen such cases, reported that the meningococcus was recovered from the blood in only two; many of his patients were found dead or died soon after admission to hospital, however, and the diagnosis was made at necropsy. *Neisseria intracellularis*, type I, is by far the most prevalent organism in acute meningococcemia; it occurs in about 90 per cent of cases. Type II A is present in 8 per cent of cases, and type II is the offending organism in less than 3 per cent. As has been stated, *Neisseria intracellularis*, type II A, was recovered from our patient by culture of both specimens of blood and material from blebs. In spite of observed sensitivity to penicillin in vitro, the organism appeared to be resistant to treatment, as shown by the prolonged illness and persistently febrile course of the patient.

This case suggests that more attention

should be paid to the status of the peripheral vessels of patients who have fulminating meningococcic sepsis and, furthermore, that the possibility of the presence of embolic or vasospastic lesions elsewhere in the body deserves serious consideration in all cases of this type.

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Salicylates in the Prevention of Erythroblastosis Fetalis*

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A RECENT editorial in *The Journal of the American Medical Association*¹ suggested that Homburger's study² of the ability of sodium salicylate to inhibit anti-Rh immunization in animals "may in time result in the development of a practical method for the prevention of erythroblastosis fetalis." While Homburger did not suggest salicylate prophylaxis for erythroblastosis fetalis in man because of the known toxicity of salicylates, the previous experience of one of us^{3,4} indicated that this should be a safe procedure if plasma salicylate levels did not exceed 400 to 500 micrograms per cc. Since the appearance of a suitable patient coincided with the publication of the above mentioned editorial, we proceeded with a trial of salicylate prophylaxis.

CASE REPORT

Mrs. M. D., a thirty year old nurse, para 1, gravida 3, had a severe blood transfusion reaction following a thoracic operation in May, 1942, and a second severe reaction in July, 1943, following a transfusion given at the time of a spontaneous abortion. She promptly became pregnant again and at an army hospital was delivered at term in May, 1944, of a stillborn, hydropic, female infant weighing 3,350 Gm. The patient claimed that an autopsy on this infant showed lesions characteristic of erythroblastosis. Postpartum, it was determined that the patient was Rh negative and her husband Rh positive. Despite the use of a vaginal occlusive diaphragm the patient became pregnant again and presented herself for management in

June, 1946. The last menstrual period had begun on March 6, 1946. The physical examination revealed a slender, white female weighing 111 pounds, height 62 inches, blood pressure 125/70, with uterine enlargement corresponding to a gestation of fourteen to fifteen weeks' duration. Blood samples from both patient and husband gave the following reactions:

Patient: Group A, MN, Rh negative, Hr' positive

No agglutinating Rh antibodies

Blocking antibody titer 1:8

Husband: Group A, MN, Rh₂, Hr' positive

It was not possible to determine whether the husband was homozygous or heterozygous with respect to the Rh factor,⁵ since no Hr'' serum was available for determination of genotype.

On June 17, 1946, the patient was started on a course of sodium salicylate, 8 Gm. daily in four doses and this was subsequently increased to 10 Gm. daily. The medication was continued for a period of twenty weeks or until delivery on November 7, 1946. Because of minor symptoms of salicylate intoxication the patient did not take the prescribed dosage regularly. Plasma salicylate levels (method of Brodie et al.,⁶) and Rh antibody titers during therapy were as shown in the table on page 662.

At no time were any agglutinating antibodies found in the maternal blood. Although the fall in blocking antibody titer starting the twenty-fourth week of pregnancy might have suggested that salicylates were interfering with antibody production, the outcome indicated a therapeutic failure. Fetal movements ceased on November 6th, in the thirty-fifth week of gestation and a macerated, stillborn, female infant weighing

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2,440 Gm. was delivered on November 7, 1946, after a labor of six hours. Autopsy on the infant confirmed the suspicion of erythroblastosis fetalis, with characteristic findings in the liver, spleen, lungs, brain and placenta. The salicylate level in serous fluid from the fetal abdomen was

Date	Salicylate Level (micrograms per cc.)	Blocking Antibody Titer (against Rh ₀ Cells)
6/28/46	201	1:32
7/1/46	222	
7/10/46	200	1:128
7/15/46	220	1:128
7/26/46	...	1:256
8/5/46	201	
8/16/46	246	1:4096
8/26/46	186	1:128
9/9/46	319	1:8
9/17/46	274	1:4
9/26/46	170	1:2
10/2/46	325	1:1
10/9/46	187	1:8
10/17/46	164	1:1
10/25/46	293	0
11/4/46	250	0

174 micrograms per cc. No blood could be obtained from the fetus, although cardiac puncture was attempted at the moment of birth. The mother made an uneventful recovery and was discharged on the fifth postpartum day. Thirty hours after delivery there were no Rh antibodies in the maternal serum, but on the tenth postpartum day blocking antibodies were present in a titer of 1:4 and a month later the titer was 1:32.

CONCLUSIONS

While the results of salicylate prophylaxis in this instance were disappointing we would not suggest the procedure be abandoned. Despite the difficulties of salicylate therapy we believe that it should be given further trial, beginning earlier in pregnancy and attempting to maintain higher blood levels of salicylate than were obtained in this patient. Certainly no other "rational" measure can be offered at present to the sensitized Rh negative mother who is eager to bear a normal child, unless the use of Rh haptens as suggested by Calvin, Evans, *et al.*⁷ can be made clinically applicable.

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Editorial

Ubiquitous Mycoses

THERE are extensive areas in the United States in which the residents are exposed to infection by pathogenic fungi. In these areas a large proportion of the population becomes infected at some time but symptoms may be entirely absent or so trivial in nature as to be overlooked. In most instances no harm results and all that remains is a specific skin sensitivity but, in some cases, healed pulmonary lesions are noted upon roentgenograms. Since the application of mass photoroentgen screening of population groups will probably increase (as the method is low in cost, easy to apply and efficient), increasing numbers of pulmonary lesions, of a type that were formerly called tuberculosis upon x-ray evidence alone, will be discovered. Thus it is necessary that physicians become more aware of the pulmonary mycoses, notably coccidioidomycosis and histoplasmosis.

The development of the current concept of coccidioidal infection is one of the more dramatic stories in modern American medical history. Coccidioidomycosis was recognized only as a rare, progressive and fatal granuloma until Gifford and Dixon¹⁻⁴ first

demonstrated that the disease is essentially benign and self-limited. The recent addition of coccidioidal erythema nodosum, which is sometimes called "Valley Fever," to the clinical picture led to the development of an epidemiologic concept that Smith⁵ has called a "true disease spectrum." The recognition that histoplasmosis, instead of being a rare and fatal disease, is a common and benign infection occurring over wide areas and in a large part of the population of some areas in the Middle West is of more recent occurrence. We may find, with increasing knowledge, that the epidemiology of histoplasmosis is not unlike that of coccidioidomycosis.

At the present time the knowledge of the biology of the coccidioidal infection is applied chiefly by physicians in the southwestern parts of the United States where the disease is common. It is known that most of the infections are not recognized and that the benign cases are infrequently referred to the etiologic agent. About one of twenty initial infections will result in coccidioidal erythema nodosum. The likelihood of dissemination or of a fatal outcome may be determined by quantitative studies of the blood serological reactions. The coccidioidin skin test is widely used and, for the most part, the reactions are interpreted soundly. During the training phases of the recent war large numbers of troops

¹ GIFFORD, M. A. San Joaquin Fever. P. 22. Annual Report Kern County Health Department for the Fiscal Year July 1, 1935 to June 30, 1936.

² DICKSON, E. C. Valley fever. *California & West. Med.*, 47: 151, 1937.

³ DICKSON, E. C. and GIFFORD, M. A. Coccidioides infection (coccidioidomycosis). *Arch. Int. Med.*, 62: 853, 1938.

⁴ GIFFORD, M. A. Coccidioidomycosis in Kern County. *California Proc. Vol. Sixth Pacific Sc. Cong. Pacific Science A.*, 5, p. 791. Berkeley, 1942. University of California Press.

⁵ SMITH, C. E., BEARD, R. R., WHITING, E. G. and ROSENBERGER, H. G. Varieties of coccidioidal infection in relation to the epidemiology and control of the disease. *Am. J. Pub. Health*, 36: 1394, 1946.

were quartered in endemic areas. Controlled epidemiologic studies were made⁶ and, as a result, we know the probable infection rate and the effect of season and of measures directed toward dust control upon the rate of primary infection in these areas. Our knowledge regarding the location of endemic areas has been greatly increased. The opportunity to study pulmonary lesions from their inception to their calcification was taken advantage of⁷ and a great deal of information has been secured concerning the natural history of the common coccidioidal cavities. It seems quite probable from the epidemiologic point of view that similar studies upon the rate of attack and initial infections of histoplasmosis would be valuable if made in areas of the Middle West and it might be possible to obtain more detailed information about the clinical picture of the primary infection. It may well be that we are now uncovering another widespread and essentially self-limited disease caused by the fungus of histoplasmosis.

During the war years many hundreds of thousands of soldiers were exposed to

coccidioidal infection in the widespread endemic areas of the Southwest. A certain number of these temporary residents have contracted the coccidioidal infection and frequently this has occurred without symptoms. In other instances the mild, initial symptoms have been overlooked or misinterpreted. Many of these individuals will be subjected to screening x-ray studies in the years to come. At Stanford University all new students have x-ray examinations of the chest and during the academic year of 1946 to 1947, clinical studies made upon students whose x-rays showed previously unsuspected lesions have revealed more instances of coccidioidomycosis than of tuberculosis. The number of lesions found which were considered to be due to histoplasmosis have almost equalled those which were considered to be arrested tuberculosis. Benign coccidioidal infections are probably now present in every part of the United States.⁸ Physicians in all areas of the country will become more aware of coccidioidomycosis and of histoplasmosis; and it is hoped that when they are confronted by a pulmonary lesion, they will consider the patient's history of residence in endemic areas and will use the appropriate skin tests.

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⁶ SMITH, C. E., BEARD, R. R., ROSENBERGER, H. G. and WHITING, E. G. Effect of season and dust control on coccidioidomycosis. *J. A. M. A.*, 132: 833, 1946.

⁷ JAMISON, H. W. A roentgen study of chronic pulmonary coccidioidomycosis. *Am. J. Roentgenol.*, 55: 396, 1946.

⁸ KURZ, E. R. and LOUD, N. W. Coccidioidomycosis in New England. *New England J. Med.*, 237: 610, 1947.

A System for the Routine Treatment of the Failing Heart*

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FOUR factors are generally considered of paramount importance in the management of the failing heart, namely, salt, water, digitalis and diuretics. Most current methods take account of these factors and put them into operation in special combinations through the use of various diets, several diuretic agents and digitalis preparations, administered in varying doses, intervals and sequence.

Several systems have been advocated in the literature. There are those in which digitalis occupies the central position. An attempt is first made to secure the results by digitalis alone, other factors being added when digitalis alone does not suffice. Methods are described in which exceedingly low sodium intake¹⁻⁴ is emphasized, and recently a system was proposed for the treatment of heart failure in which huge quantities of water play a conspicuous rôle.^{5,6}

In the systems which are most commonly employed, the "low-salt" diet is prescribed, water intake is curtailed and considerable dependence is placed on oral diuretic agents, the mercurial diuretics being reserved for the more advanced cases with frank signs of edema or effusions and injected at inconstant and infrequent intervals. While the prevailing plans embodying these factors have taken us a long way from the days when the phrase, "rest, digitalis and futility,"

fairly described what was in store for the victim of congestive failure, the current plans and the methods by which they are applied seem still to leave the treatment of congestive failure short of the full potentialities for control.

The results obtained by the prevailing routines in the treatment of congestive failure have not been systematically evaluated in recent years. We have undertaken to make such an analysis of the results in 502 admissions treated by methods prevailing in four large hospitals, representing a fair cross section of the practice in New York City. We have compared these with the results obtained in 140 similar admissions treated by a system which we have applied in the past few years, involving the simultaneous use of digitoxin and measures for dehydration in which salt, water and the mercurial diuretics are balanced in a regimen conveniently applicable in a routine manner.

THE METHOD

Routine. The patient is put at rest, either in bed or in a chair, depending on the patient's comfort, unless there is some factor requiring bed rest alone, as in acute coronary thrombosis. Bathroom privileges are permitted if the patient is equal to the effort. The diet consists of 4 to 6 glasses of milk

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daily and the water intake of 2 to 3 quarts taken in drinks of a few ounces at frequent intervals throughout the day. If no digitalis has been taken recently, a single dose of 1.2 mg. of digitoxin is given at one time. This is followed by a single daily dose of

omitting those known to be especially high in sodium content. No salt is used in cooking and no salt is added at the table. This increase in the diet may produce slight and gradual increase in body weight. The daily dose of the mercurial is continued until the

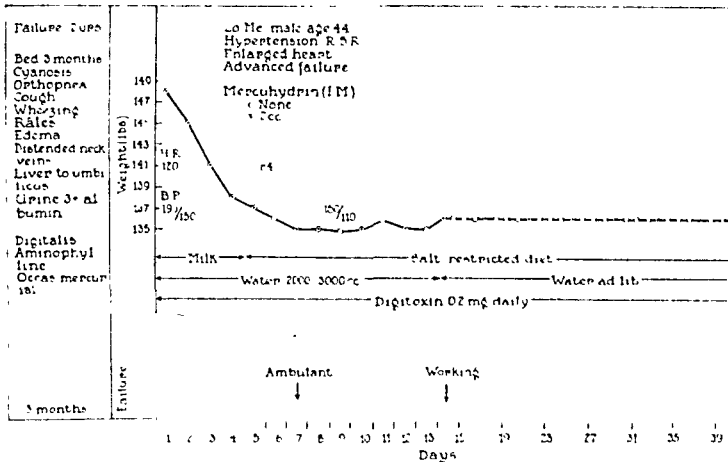


FIG. 1. Typical response of advanced congestive failure to the proposed regimen. The salt-restricted diet represented approximated 3 Gm. sodium chloride daily. The patient had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission.

0.2 mg. The maintenance dose is increased or diminished according to indications. The patient is weighed at the outset and a chart is kept of the daily weight. A dose of mercurhydrin is given intramuscularly, 0.5 cc. on the first day. If there are no untoward reactions and the diuresis is insufficient, the dose is increased to as high as 2 cc. daily. The foregoing regimen is continued until all signs of edema subside and the weight declines to a resistant level, the "dry weight." At this point, the continued use of the daily mercurial fails to produce any substantial further reduction in weight. After a few days to insure that the "dry weight" has been reached, the patient may become ambulant and the treatment is modified to establish the maintenance requirements.

The daily weight is also the chief guide to adequate maintenance. In adjusting the regimen for maintenance, a more liberal diet is introduced, containing most of the common foods (eggs, meat, cereal, sugar, fruits, vegetables, cream, sweet butter) and

weight shows a tendency to level off either at the original "dry weight" or at a somewhat higher level. The interval between the doses of the mercurial is then prolonged to every other day. If the weight level is maintained after a few doses, the interval is prolonged to every third day for a few days. This plan of prolonging the interval between injections is pursued until a point is reached at which a fairly abrupt rise in weight occurs on the day before the injection or a conspicuous fall on the day after the injection. One then returns to the longest interval which suffices to prevent these changes. In this manner, the maintenance plan for the mercurial is established.

In the course of time, it often becomes possible to liberalize the diet further and even prolong the interval between the mercurial injections. The maintenance of a constant body weight with only slight fluctuations and without any abrupt peaks of weight rise or fall is the primary indication that the maintenance regimen is adequate to insure against recurrence of congestive

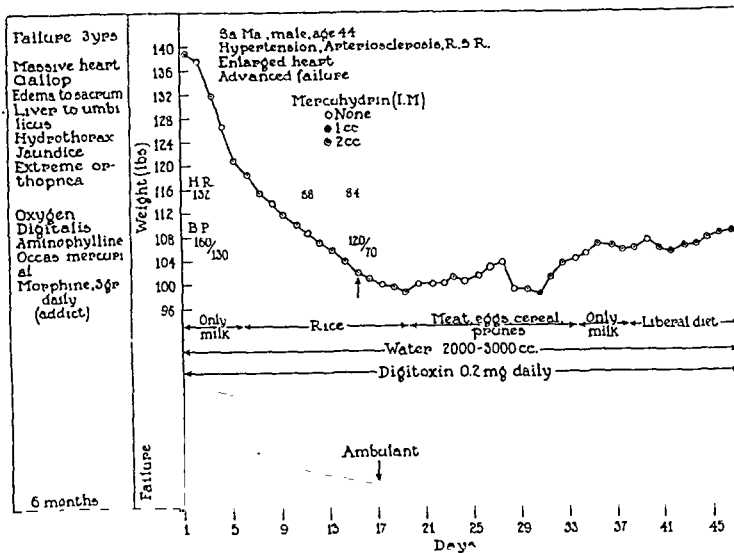


FIG. 2. Typical response of advanced congestive failure to the proposed regimen. The patient was a physician. He had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission. The rice was added to the milk diet because he was distressed by his hunger. He had advanced pyorrhea and at the ↑ on the weight curve, bleeding from several sockets appeared which was difficult to control. The blood tests and prothrombin time were normal. The mercurial was suspected as the cause. After one week it was finally checked by local measures although the mercurial was continued. Note that the weight began to rise when the diet was increased and the interval between injections prolonged. The intensification of treatment proved that it was due to fluid. The patient became ravenously hungry and his weight again began to increase as a result of increased food intake. That it was not due to water this time was evident from the failure to lose weight with the more intensive system of dehydration (milk and the daily mercurial).

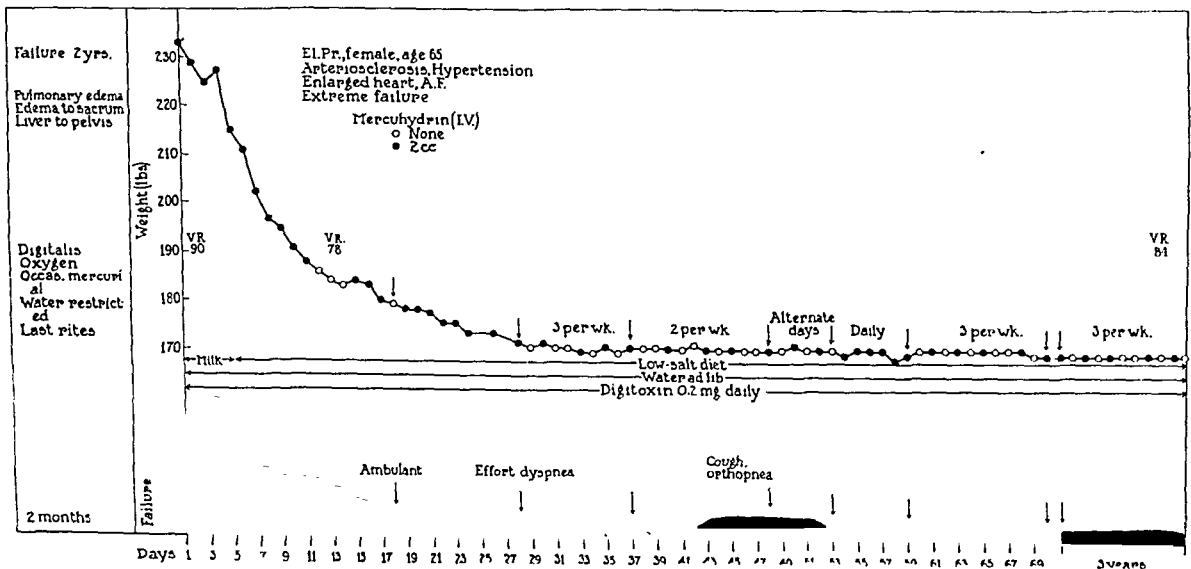


FIG. 3. Typical response of extreme congestive failure to the proposed regimen. The patient had been fully digitalized (to the point of vomiting and coupling) and was receiving a daily maintenance dose before admission. Note the intensification of symptoms in first four days of treatment; only the rapid fall in weight allowed the prediction that recovery was likely. Note the system of trial and error for establishing the maintenance program. The patient was working during the years of maintenance.

failure. This regimen is continued indefinitely. Illustrative cases are charted in Figures 1 to 5.

Special cases require variations in this routine. The size of the dose of the mercurial may be reduced and the intervals between

they develop shortness of breath and pulmonary râles with or without other signs of congestive failure. Digitalis alone is not very effective in controlling the failure in these cases. We apply the method outlined above except for the daily weighing. In

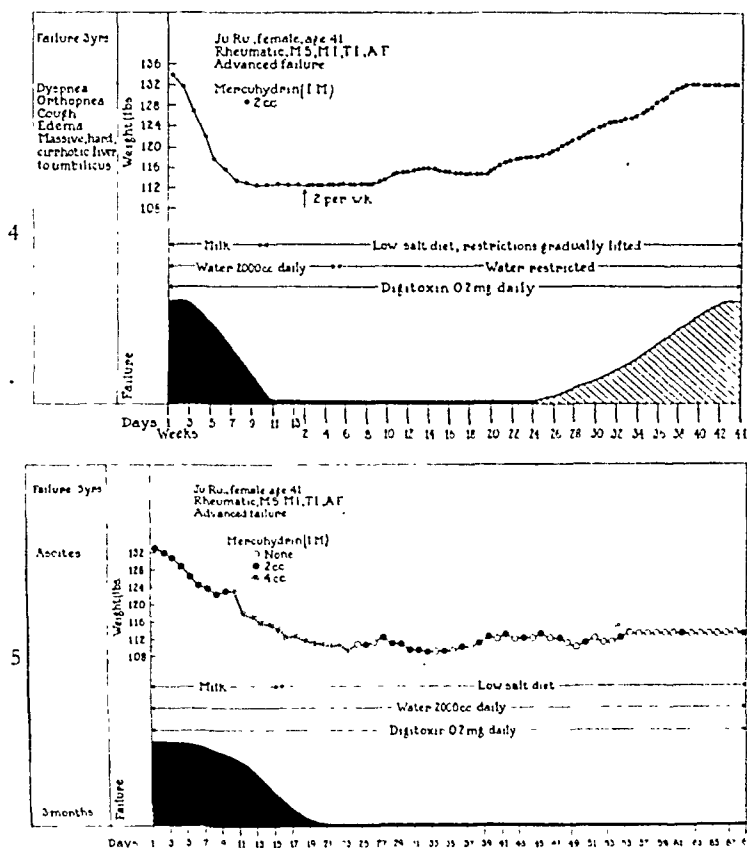


FIG. 4. Typical response of advanced congestive failure to the proposed regimen. The patient had been fully digitalized and was receiving a daily maintenance dose of digitalis before admission. Note that while the patient remained essentially free of former signs and symptoms of failure during the long maintenance period, the gradual increase of salt intake was accompanied by the appearance of ascites. (Fig. 5.)

FIG. 5. Same patient as in Fig. 4. Note that ascites was now the only sign of failure and that it takes longer to clear it than respiratory signs and edema. Note also the leveling off of the weight with the 2 cc. daily dose and the resumption of the decline when the dose was increased to 2 cc. every twelve hours.

doses prolonged with the appearance of the slightest evidence of excessive dehydration; and since the signs and symptoms are often indecisive at the beginning, it is well, when in doubt, to interrupt the dehydrating program temporarily. The case of acute coronary thrombosis requires special attention. Some of these patients develop pulmonary edema in association with the acute coronary thrombosis or, in the ensuing days,

addition to the other measures, the patient receives a daily dose of the mercurial until signs and symptoms of failure subside. The interval between injections is then usually prolonged to three days. This may be continued until it becomes possible to determine the necessary interval more precisely by the guide of the body weight. The subsequent course decides the need for the continued use of the mercurial diuretic. It is not un-

common that, after recovery from the effects of the acute occlusion, these patients are able to carry on satisfactorily without any treatment for congestive failure.

In brief, five factors of cardinal importance are embodied in the proposed regi-

between what is prescribed and what the patient actually receives. It is not at all uncommon that a patient on a so-called "low-salt" diet in the hospital finds his food so highly palatable that he, himself, becomes suspicious of its being literally

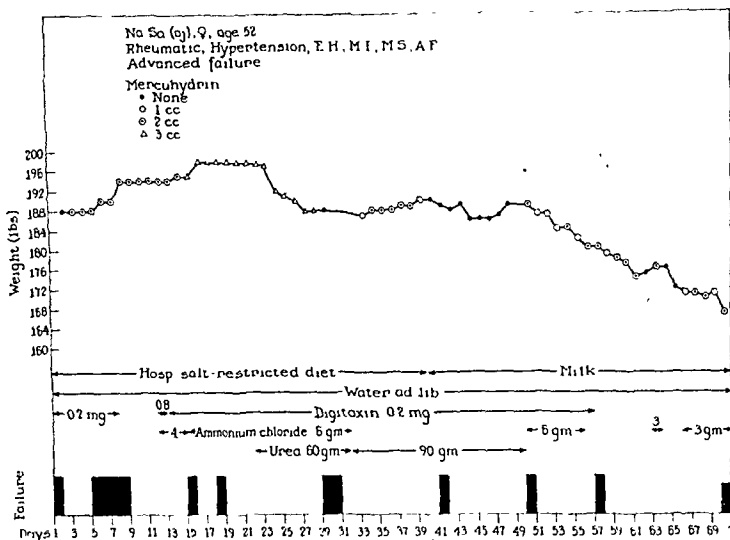


FIG. 6. Importance of adequate salt restriction in advanced congestive failure. Note that in spite of 3 cc. of the mercurial daily in addition to various oral diuretics, the loss of edema was insignificant until the salt was restricted to 1.5 Gm. by means of milk.

men: adequate salt restriction, liberal water intake, mercurial diuretics, digitoxin and a chart of the daily weight as a guide to the optimal state. The program calls for the application of these factors in two phases: (1) in the attack to abolish congestive failure and establish an optimal state and (2) in the long period of maintenance to prevent the recurrence of congestive failure.

Diet. The prescription for a "low-salt" diet has now become a fairly common procedure in the treatment of congestive failure. The so-called "low-salt" diets of most hospitals contain anywhere from 3 to 6 Gm. of sodium chloride. This is too much salt for a great many patients with advanced congestive failure; and because of the wide variation in the salt intake from day to day with such a diet, the course of the response of the failure becomes irregular, the patient showing a fairly marked response on one day and almost none the next. This type of attempt at salt-restriction, in our experience, is unsatisfactory. There appears to be a wide gap

"loaded" with salt, and the salt shaker not infrequently appears on the tray. This might suggest exceptionally incompetent dietary service, but the fact remains that, in relation to salt-restriction, these deficiencies prevail in abundance in the routine management of congestive failure in hospitals whose general standards of performance are otherwise considered very high. The traditional belief that salt is a harmless article of diet is not easy to overcome, and it will require a great deal of intensive education to impress upon the dietary and nursing services of hospitals the fact that an extra gram of salt may actually be a poison in many patients with congestive failure. The difficulties of securing a "low-salt" diet are not sufficiently appreciated by physicians; they often declare that their patients failed to respond even though they were on a "salt-free" diet without realizing how imperfectly the order for a "salt-free" diet was actually being carried out. (Fig. 6.)

It is for these reasons that we advocate the

use of milk as the sole article of diet in the early days of a course of treatment for congestive failure. The value of milk as a diuretic agent has long been known.^{7,8,9} The 1 to 1.5 liters of milk a day supplies about 800 to 1,200 calories and from 1 to 1.5 Gm. of salt. The capacity for salt excretion is rarely below this level in cases of failure. Aside from a sense of hunger, most patients encounter no difficulty in taking this quantity of milk. They usually cooperate well in this restriction of diet, especially since, in the majority of cases, it is not necessary to continue it beyond five to seven days. The few patients who show special intolerance for milk, developing nausea or diarrhea, of course, have to be managed with one or another of the "low-salt" diets which are more troublesome to arrange.^{1,5,10} In such cases, salt substitutes which are free of sodium, sprinkled on the food, may be used to advantage. For patients who are distressingly hungry with the milk alone, a bowl of boiled rice with sugar and milk several times a day may be added. Dry rice contains only about 0.1 per cent sodium chloride. There are about 350 calories in 100 Gm., and patients take from 200 to 300 Gm. daily in the so-called "rice diet" for hypertension.¹¹

Supplementary Measures. There are several supplementary measures which are sometimes applied in addition to the foregoing regimen. Sedation is not used routinely but to meet special requirements. Patients in a poor nutritional state or those with massive edema, likely to lose 20 or 30 pounds of edema fluid, may receive supplementary vitamins, especially 10 or 20 mg. of thiamine chloride daily because intensive diuresis may result in deficiency.

Water. In the traditional methods for the treatment of congestive failure, water intake is restricted. The extent of the restriction varies greatly. Most systems call for the reduction of water intake to about 1,000 cc. a day, and often the intake is as low as 500 cc. or less. Such restriction seems entirely natural to patients with edema who know that they have too much water in the body;

many of them have been so strongly impressed with the danger of water that they are willing to endure much discomfort from thirst because of their conviction that water in the presence of edema is harmful. Indeed, this conviction receives support when the patient, inappropriately treated in other ways, allows himself a more liberal intake of water; for, unless salt restriction is adequate, a liberal intake of water will increase the edema.

There are several important studies in the literature relating to the problem of water restriction in cardiac failure. Since the details of the relationship between salt and water have been abundantly discussed and reviewed in the past few years,^{1,2,5,10,12} it will suffice at this point merely to call attention to a few of the physiologic facts which serve as the basis for the procedure employed in the present study. A normal person taking a liberal quantity of water may excrete it in about four hours, but will take twenty-four hours or longer to excrete the water if salt has been added to it. The excretion of water is conditioned, therefore, by the presence of salt. A normal individual (quiet occupation in a comfortable atmosphere) requires about 1,500 cc. of fluid daily to make up for water losses (vapor, sweat, urine, stool) and prevent accumulation of blood metabolites or cellular dehydration; patients with damaged kidneys may require nearly twice as much.¹³ The vast majority of patients with heart failure have no difficulty in excreting water *per se* but have a subnormal capacity to excrete salt.^{1,2,8} The salt retention leads to water retention and edema. Whereas the average normal individual consumes and is able to excrete 10 or more Gm. of sodium chloride daily, the patient with heart failure in the more advanced stages may retain salt even if the intake is as low as 2 Gm. a day. When, in such a patient, the salt intake is restricted to the capacity for salt elimination, the quantity of water becomes a matter of indifference within limits; he will excrete it all whether the intake is 800 cc. or 3,000 cc. Water is a diuretic, and an effective plan for the treatment of congestive failure has

been described which includes the administration of water in amounts up to 6,000 cc. or more daily.⁵

In the treatment of congestive failure, therefore, it is clear that with appropriate salt restriction there is no need for water

In our experience, 2 to 3 liters of water daily can be taken conveniently and appear to be sufficient in the vast majority of patients with failure. It is surprising to learn how little water patients are apt to consume without special supervision. (Fig. 7.) In the plan

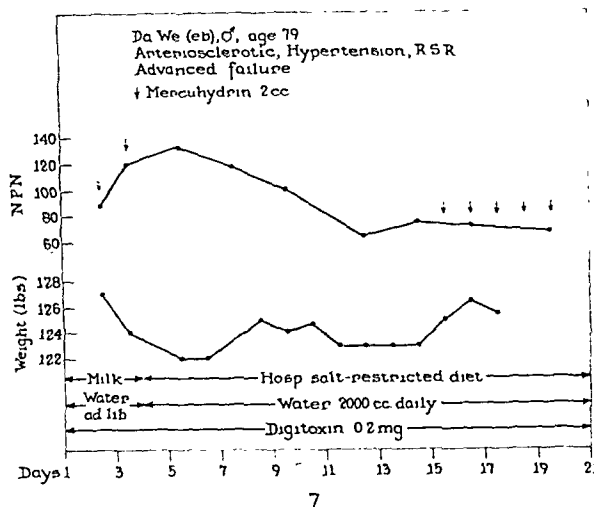
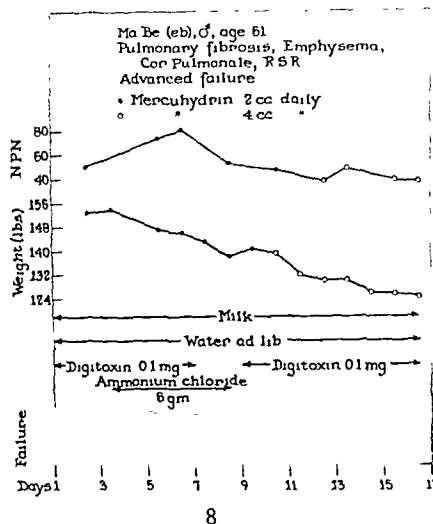


FIG. 7. Importance of adequate water intake in preventing rise of blood non-protein nitrogen during treatment of congestive failure. The order for water *ad libitum* resulted in an intake of only about 500 cc. daily and two doses of the mercurial were attended by a rise of the non-protein nitrogen from 83 to 133 mg., but during the intake of 2,000 cc. water daily there was no rise in the non-protein nitrogen after five doses of the mercurial.

FIG. 8. Note that with the 2 cc. daily dose of mercurhydrin the weight curve leveled off but resumed the fall when the dose was increased to 4 cc. daily. Note the temporary rise in blood non-protein nitrogen with a secondary fall even when the dose was doubled.



restriction; and furthermore, enough water must be given to maintain sufficient renal function to excrete the large quantities of extracellular fluid (edema) which is not only water but a solution of solid materials in water.

In the proposed regimen for the treatment of congestive failure, it is planned to allow a liberal intake of water sufficient to enable the kidneys to clear the blood of metabolites, taking account of the increased amount of such materials which come from the edema fluid. It is not intended that the water intake shall serve as a diuretic to any significant degree because for that purpose quantities are necessary which are troublesome to consume. Theoretically, the patient's thirst might decide the amount of water which is taken, but practically, such advice does not serve the purpose because of the tendency for patients with edema to take too little water, in spite of their thirst.

of treatment, therefore, it is often necessary to request the nurse or the attendant to administer the water at fixed intervals in order to insure that a sufficient quantity is taken.

Digitoxin. Any one of a large number of digitalis preparations may be used to produce effective digitalization. For patients in extremis, the material may be given intravenously; a single dose of 0.4 mg. of ouabain, 1 mg. of digoxin, 1 mg. of cedilanid, or 3 U.S.P. units of any injectable digitalis preparations, such as digifoline, may be counted upon to produce a fairly high degree of digitalization. Additional fractions may be given at intervals of two hours if necessary.

In the vast majority of cases the oral route suffices, and for these, digitaline Nativelle or digitoxin is the material of choice. As has been shown in several reports,¹⁴⁻¹⁷ this glycoside, after oral administration, develops

its full action as quickly as digitalis leaf or the tincture and its duration of action is the same as that of digitalis. While in the case of digitalis only about 20 per cent of the active glycosides are absorbed, the absorption of digitoxin is virtually complete. An average full digitalizing dose of 1.2 mg. may be safely given at one time to patients who have not recently had digitalis. This dose will produce a high degree of digitalization in about 75 per cent of the patients in congestive failure in a period of about six to ten hours. The incidence of systemic toxicity with this dosage is extremely small (less than 2 per cent). A therapeutically equivalent dose of digitalis leaf (1.2 Gm.) or the tincture (12 cc.) cannot be given in this way because the large quantity of non-absorbable glycosides will irritate the stomach sufficiently to cause nausea or vomiting in 20 per cent of the patients. In the case of the more tolerant patients, additional doses of 0.2 to 0.4 mg. may be given at intervals of six hours. A daily maintenance dose of 0.2 mg. serves the largest proportion of patients although in some the dose may have to be reduced to 0.1 mg. or increased to 0.3 mg. daily to maintain the optimum level of therapeutic effects.

For the case of those patients who have been partially digitalized with digitalis and for whom it is planned to turn to digitoxin, the potency ratio of 1 to 1000 is to be remembered; digitoxin is approximately 1,000 times as potent as U.S.P. digitalis by oral administration; 1 mg. of digitoxin may be used to produce the effect of 1 Gm. of digitalis.

Diuretics. Since an increased amount of extracellular fluid is characteristic of all patients with congestive failure, the indications for a diuretic agent exist in all of them. For oral administration, there are many such agents, namely, the xanthines, the acid-forming diuretics like ammonium chloride and urea. While some patients tolerate these agents fairly well, in the vast majority, tolerable doses are not very effective, and those doses which are sufficiently effective give rise to disagreeable symptoms in a high

proportion of patients with failure. Urea is often necessary in doses as high as 90 Gm. a day. It has an unpleasant taste and such doses give rise to gastrointestinal symptoms and drowsiness. Ammonium chloride exerts its action by shifting the acid-base equilibrium toward the acid side. While daily doses of 3 to 4 Gm. are usually well tolerated, the more effective doses of 6 to 8 Gm. or larger not infrequently act as laxatives and cannot be continued for sufficiently long periods of time. Occasionally, an alarming state of renal acidosis results. Similar objections apply to the xanthines, theophylline or aminophylline. In small doses they are well tolerated but highly effective doses too frequently result in cerebral stimulation and gastrointestinal distress, so that their use must be discontinued after varying periods of time.

It is for these reasons that the mercurial diuretics are used almost exclusively in the proposed system of treatment. They are the most effective of all the diuretics. We prefer the intramuscular injection because of greater safety. The few recorded deaths with mercurial diuretics have all occurred with intravenous doses.^{18,19} The danger of the intravenous dose, however, is relatively slight; and if the patient is one who reacts by the formation of lumps after the intramuscular injection, the slow intravenous injection may be substituted.

As to the site of injection, we usually prefer the muscles of the buttock; but it is well to explore other areas; many patients find the more accessible areas of the thighs and arms quite satisfactory for relatively painless injections. Emphasis should be placed on the need for making the injection deep into the muscles; the deeper the injection, the less is the likelihood of lump formation.

We prefer the preparation mercurhydrin to either mercuzanthin (mercuophylline) or salyrgan-theophylline (mersalyl and theophylline) because of the fact that it is less irritant to the muscle and is less apt to produce pain.²⁰ If the patient is hypersensitive to one of the mercurials and de-

velops allergic reactions, another mercurial diuretic may be substituted.²¹

The treatment is started with an initial dose of 0.5 cc. in order to ascertain the responsiveness of the patient and hypersensitivity. The most favorable plan is one in which the patient loses about 3 pounds a day. If this occurs with 0.5 cc., that dose is repeated daily. If the diuretic response is too small, the dose may be increased to 2 cc. daily. There are occasional patients in whom even the 2 cc. dose is inadequate or becomes inadequate after the first few doses. In that event, we have administered as much as 4 cc. daily, 2 cc. at twelve-hour intervals. (Figs. 5 and 8.)

The site of action of the mercurial diuretic is not conclusively established, but the best evidence indicates that it acts on the renal tubules to diminish reabsorption; and in view of the fact that there is a large increase not only in the total salt output but also in the concentration of salt in the urine,^{22,23,24} diminished salt reabsorption may be a primary effect.

One of the most common unfavorable responses is weakness and muscle cramps. These are not usually due to the nature of the diuretic agent but to excessive diuresis and salt loss. Some patients may lose as much as 10 pounds of extracellular fluid from one injection without unpleasant symptoms whereas in others as little as a two- or three-pound loss at one time is excessive and results in intense weakness. The acute symptoms are sometimes overcome by half a teaspoonful of ordinary table salt. Their recurrence may often be prevented by the use of smaller doses of the diuretic. The common practice of prolonging intervals between doses in these cases is to be discouraged for this does not tend to eliminate the unpleasant responses. In point of fact, prolonging the interval between doses tends to increase the unpleasant reaction because it is the abrupt shift in electrolyte and water balance which gives rise to these symptoms; and after more fluid has accumulated, the diuretic response to a given dose may be larger. It is our practice

to maintain the interval unchanged or to shorten it, but to diminish the dose so as to maintain a more or less constant diuretic effect without abrupt and extreme fluctuations.

One question which frequently arises is that of using the mercurial together with ammonium chloride. Since the object of such a combination is to enhance the diuresis,^{25,26} we rarely use it; the mercurial alone suffices to produce all the diuresis that is necessary. If no weight loss occurs after several days on the routine, in which appropriate doses of the mercurial alone were used, ammonium chloride may be added.

The routine plan calls for a daily dose of mercuhydrin. This appears to be safe in the presence of an average normal urine flow. The excretion of the mercurial diuretic has not been extensively studied; but there are some unpublished experiments in the dog which show that about 90 per cent of the mercury may be recovered in the urine in a period of about six hours in the case of mercuhydrin, and observations in the rabbit²⁷ with salyrgan-theophylline and mercupurin indicate nearly complete elimination within twenty-four hours. In the extensive experience which we have had with patients in congestive failure and in patients with arterial hypertension without failure, there has been no indication of significant cumulation after daily injections of mercuhydrin for periods of weeks.

The possibility of renal damage or other toxic effects²⁸ by the organic mercurial often restrains physicians from its use. Although there are several suggestive reports of renal damage,^{18,29,30} the evidence for irreversible injury of the kidney by the therapeutic doses of these non-ionized forms of mercury is far from convincing. We have now had experience with fairly large numbers of patients with congestive failure receiving 2 cc. of the mercurial two or three times a week for periods of from six months to three years, and 3 patients who had received a daily dose for periods of from two to three years, without evidence of renal damage. Others have reported long con-

tinued use of the mercurials without harm.³¹ There is no evident contraindication to a dose of the mercurial in patients with congestive failure regardless of the state of the kidneys. Our system of continued mercurial administration has been applied to

A/G ratio 1.5, hemoglobin 7.9 Gm., CO₂ combining power 19 volumes per cent, ulcerative stomatitis, vomiting, optic neuritis, which had progressed to almost complete blindness, and muscle twitching verging on convulsions). This condition was com-

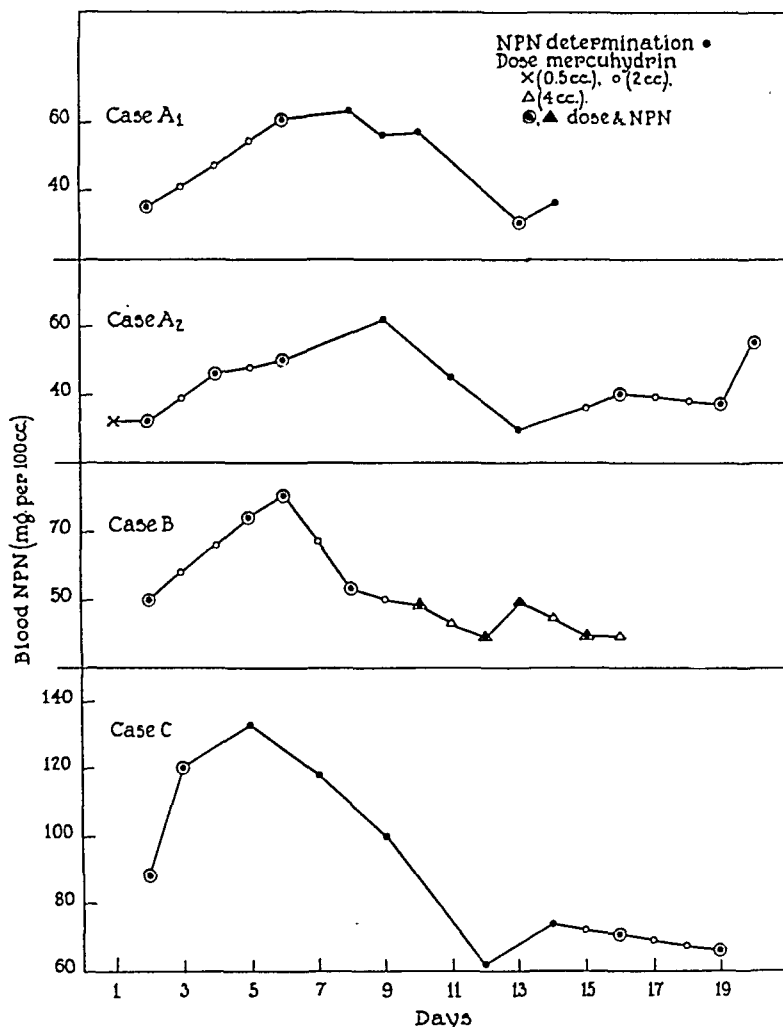


FIG. 9. Three illustrative cases showing behavior of blood non-protein nitrogen during the use of the daily dose of the mercurial in the treatment of congestive failure. Case A₁ and A₂ are repetitions in the same patient.

patients with all the common types of renal abnormalities encountered in rheumatic, arteriosclerotic and hypertensive heart disease with advanced congestive failure. We have encountered no convincing evidence of renal injury. We had one patient, a female, fifty-eight years old, with chronic glomerulonephritis and uremia (urinary casts, albuminuria, blood N.P.N. 216, creatinine 12.8, blood calcium 5.2, total proteins 6.1,

plicated by congestive failure and pulmonary edema. The failure was controlled by digitalis and three intravenous injections of 1 cc. of mercurpurin. After four weeks, she was discharged with virtually complete clinical recovery (free of symptoms, CO₂ combining power 43); there remained the laboratory findings of renal failure (blood N.P.N. 106, creatinine 5.6, blood calcium 7.8).

Whether the administration of the mercurial is continued in congestive failure will be decided by the nature of the response. Obviously, if a patient has a marked oliguria excreting only a few ounces of urine per day and a few doses fail to produce a substantial increase, there is no point in continuing. In the absence of a therapeutic response, toxic cumulation may occur. Attention should be called, however, to the need of making sure that the trial doses were adequate before the mercurial is discontinued.

The daily administration of the mercurial may result in an elevation of the blood N.P.N. Azotemia has been noted by others.³² We have not followed the course with sufficient blood N.P.N. determinations in our cases to ascertain the frequency of this phenomenon. In a group of 133 patients treated with a daily dose of the mercurial, it was encountered in twelve patients. Figure 9 shows some typical examples. The mechanism of this effect is imperfectly understood. It is sometimes prevented by insuring adequate water intake. It may disappear during the continued use of the drug and sometimes even when the dose is increased. The effect appears to be reversible in much the same way as the action on the tubules which impairs reabsorption of salt and water, accounting for the therapeutic results. Within a few days after the mercurial is discontinued, the blood N.P.N. returns to normal levels. Until the mechanism of this response is better understood, it is well to follow the course with blood N.P.N. or urea determinations, especially in those cases in which the daily injection is to be long continued, and interrupt the dose for a few days if a marked rise occurs and tends to progress, resuming the injections at longer intervals.

One of the objections which has been offered to the use of the mercurial in our plan of treatment is the fact that it must be given by injection. The oral tablets and the rectal suppositories rarely suffice because in most cases, while small doses may be tolerated for a long time, adequate doses soon produce

gastrointestinal distress, nausea, vomiting, diarrhea and abdominal cramps so that its continued use must be interrupted. It seems, however, that too much weight is given to the difficulty of the injection. It is well to bear in mind the similarity in the problems of diabetes and congestive failure. Both require continued injections to keep the conditions under control. There is little more trouble in the injection of the organic mercurial than in the injection of insulin. After an appropriate system of intervals has been established by the physician, a member of the family and sometimes the patient can make the injection of the mercurial with little or no danger.

Guides to Treatment. The guides to the treatment of congestive failure, which are employed in most current methods, are the patient's symptoms, the extent of the edema and a charting of the fluid intake and urine output. These are, on the whole, unsatisfactory in our experience. The patient with far advanced congestive failure may, in the early days, show no appreciable amelioration of symptoms with a system of treatment which is eminently satisfactory. The absence of early relief of symptoms often leads the physician to abandon a course of treatment which, if pursued, would have produced the desired results. (Fig. 3.) Fluid balance charts are notoriously misleading. At their best, they fail to take into account variations in visible and insensible perspiration and other sources of water loss. At their worst, and much of such charting approaches that state quite closely, the quantities of fluid or urine are estimated rather than measured and many of the fractions fail to be recorded. It is a time-consuming and troublesome nursing procedure which does not yield information justifying the effort; as a routine in the treatment of congestive failure, it should be abandoned. In its place, we employ a chart of the daily weight. Most patients with congestive failure are equal to the effort of a daily weighing. Long before symptoms improve or gross signs of edema have changed, the declining body weight reveals that the treatment regi-

men is effective (Fig. 3) and allows the prediction that the failure will be brought under control; and conversely, a leveling off of the curve of weight loss, while edema persists, indicates at once the need for intensification of the treatment. (Figs. 5 and 8.) The treatment of congestive failure without an accurate record of body weight is comparable to the treatment of infection without a fever chart, or the treatment of auricular fibrillation by digitalis without a record of the changes in heart rate, or the treatment of diabetes with insulin using only symptoms as a guide and no record of changes in the ketonuria or glycosuria. Without this record of weight, the treatment of congestive failure is deprived of all the precision that is otherwise possible. (Fig. 10.)

The current routine treatments of congestive failure are not systematically guided by the chart of daily weight. In the 502 admission for congestive failure, which we shall discuss presently, there were only 2,299 weighings for a total of 11,873 hospital days, or a weighing on less than 20 per cent of the hospital days. Of these 502 admissions, 51 per cent were not weighed at all; and in the remaining 49 per cent, who had some weighings, the interval between them averaged 3.1 days. Since it is not often done, the technics are poorly developed. Those who have not been in the habit of prescribing a daily weighing for their patients with congestive failure have an interesting experience in store for them when they begin to write such orders and begin to depend on the record from day to day; either the scale is out of order or inaccurate, or it is not readily accessible to the patient, or there are not enough scales for the number of patients, so that it becomes impractical to weigh at approximately the same time each day, or the patient is frequently weighed on different scales varying in adjustment by several pounds, or the nurse forgets to weigh the patient every day (although a lapse in the daily temperature recording is a rare occurrence), or the nurse weighs the patient but fails to record it or records it among the nurse's notes making the daily inspection of

the course too time-consuming to be useful. To weigh a patient accurately daily and to keep an accurate chart of the weight seems to be either a lost art or one which has never been well developed.

The objective is to reduce the body weight to a level at which the optimum volume of extracellular fluid remains. In actual practice, the proposed system is continued until the patient ceases to lose weight. We term this the "dry weight." Many patients are most comfortable at that level. In others, the "dry weight" represents excessive dehydration and the patient feels stronger at a level a few pounds above it. The character of the symptoms helps to decide the weight at which the patient will be maintained.

Lapses in restrictions are extremely common. They are revealed in an abrupt rise in weight usually long before any symptoms occur, although in patients with predominantly so-called "left heart failure" an increased dyspnea or othopnea sometimes precedes a significant rise in weight as evidence of lapse in treatment.

In the long period of maintenance, the problem sometimes arises of distinguishing an increase in body weight due to improving appetite and health from that due to water retention. An abrupt rise of a pound or two is strongly suggestive of water retention. When there is doubt, the problem can frequently be resolved by intensification of the treatment through a daily injection of the mercurial. (Fig. 2.) If it is good body tissue, such a measure is apt to produce little change in the sustained level of the body weight. (Fig. 11.)

Maintenance. The need for an effective system of maintenance after recovery from an attack of congestive failure is self-evident. Unless that is done, the patient again passes into congestive failure. Among the 376 patients with congestive failure treated with the various current routines, there were sixty-nine patients or 18.2 per cent with multiple admissions to the same hospital for the treatment of failure. The number of admissions varied from two to eleven in different patients, an average of

2.8 admissions per patient at an average interval of 8.2 months. There are many causes for the recurrence of attacks of failure. The majority of recurrences are preventable. Lack of cooperation on the part of the patient is not an uncommon cause but we

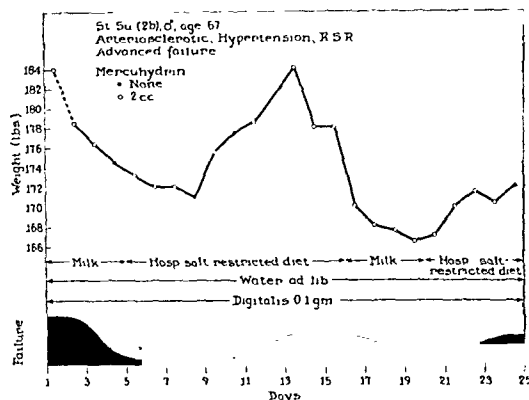


FIG. 10. Importance of daily weight as guide to treatment in congestive failure. Note that the daily mercurial and the milk diet caused prompt recovery; there was prompt relapse when the interval was prolonged and the salt intake increased. Note that the sequence of adequate and inadequate routines was repeated and the patient was well on the way to a third attack of failure at the time of discharge. Although the patient was weighed, the record was not used as a guide to therapy.

believe that a very considerable proportion of the recurrences may be assigned to the inadequacy of the therapeutic plan for maintenance with which the patient is provided. In the most common current practices, after the patient has recovered from an attack of failure the diet is made more liberal, although salt may still be restricted and digitalis is likely to be continued; but there are two common failings, namely, dependence is placed chiefly on oral diuretics, if they are used at all, and the patient's symptoms are used as a guide to adequacy of treatment. The oral diuretics are usually insufficient and to discover that the treatment is inadequate when symptoms appear is too late. A frequent modification that is equally bad is to have the patient return for an injection of a mercurial when the legs begin to swell or suffocation appears at night. These are not systems of maintenance but of retreatment of failure. The omission of the maintenance schedule of the mercurial

diuretic is a frequent cause of recurrence of congestive failure. (Fig. 12.)

It is our practice to depend on the same five cardinal factors in maintenance as during the treatment of the attack of failure: Salt is restricted, water is taken freely, a

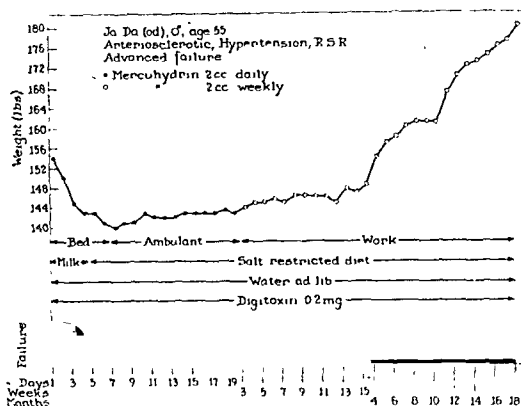


FIG. 11. Typical response of advanced congestive failure to the proposed regimen. Note the period of 1.5 years of maintenance with 2 cc. mercurhydrin per week; weight gradually rises due to good body tissue, not significantly lowered by periodic trial with daily doses of the mercurial. Compare with Figure 12.

daily dose of digitoxin is continued and the intramuscular mercurhydrin is continued. The charting of the weight serves as the guide. The details vary from one patient to another and the final plan for any one patient is determined by the method of trial and error. The objective is to discover the most liberal diet and the longest interval between injections of the mercurial which will serve to maintain the patient's weight at a constant level or with slow rise which is not lowered by intensification of the treatment. The various measures are interrelated and may be balanced. The patient often has a choice of maintenance plans such as a highly unpalatable diet containing only 2 Gm. of salt a day together with only one mercurial injection a week or a combination of a very liberal diet with a mercurial injection every other day.

At this point, attention should be called to a common misconception regarding the manner in which the mercurial functions during the maintenance period, namely, the belief that the mercurial fails to serve a purpose when the dose fails to produce a fall in

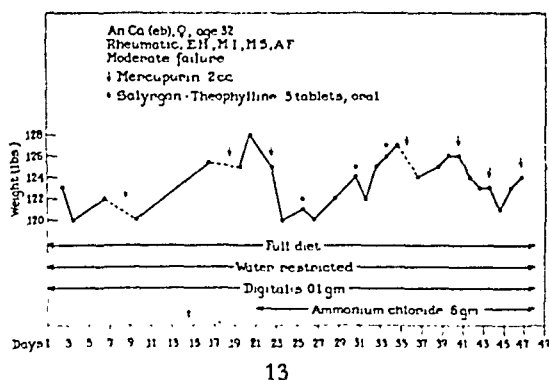
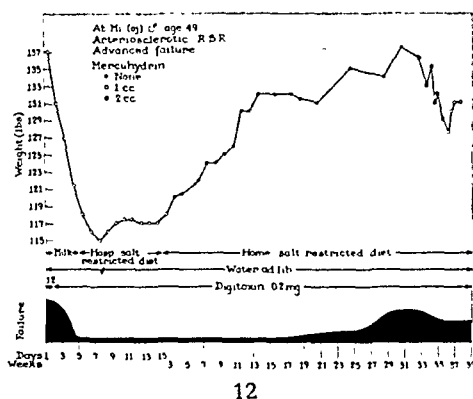


FIG. 12. Importance of the maintenance dose of the mercurial diuretic. Compare with Figure 11. Note the gradual rise of weight due to fluid, followed by symptoms of failure when the maintenance dose of the mercurial was interrupted.

FIG. 13. Type of response of congestive failure to current methods of treatment.

weight. On the contrary, it is precisely the object of the maintenance doses to maintain such a constant urine flow that the weight curve will tend to show only minimal fluctuations. If the doses are properly spaced, a daily water balance will be maintained at the optimum level. Under these conditions, the dose of the mercurial will serve its function without producing greater urine flow (as shown by the fall in weight) than was present on the previous day. An example may serve to clear the point: A physician used a daily dose of mercurhydrin in one of his patients until the weight declined from 150 to 135 pounds. Symptoms and signs of failure subsided. When a few additional daily doses failed to reduce the weight below 135 pounds, he prolonged the interval between doses to every four days. As a result the body weight rose to 139

pounds before each injection and each injection produced a prompt loss of 4 to 5 pounds, giving rise to unpleasant symptoms, chiefly prostration. In this case, a reduction of the dose to 1 cc. and the interval to every two days resulted in a constant weight of 135 pounds with negligible fluctuation and the prostration after each dose vanished. Again, there is the similarity between the problem of insulin in diabetes and the mercurial in congestive failure. In diabetes, it is not considered proper therapy to allow the patient to develop glycosuria, ketonuria and symptoms and then attempt to abolish them periodically by a dose of insulin. The plan for insulin is so worked out as to maintain the patient free of symptoms, free of ketonuria and free of glycosuria (or at a

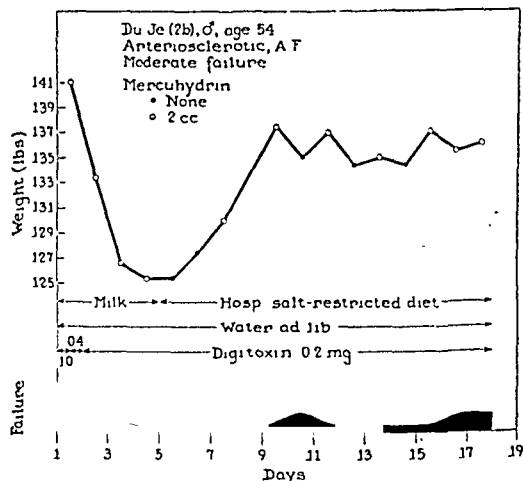
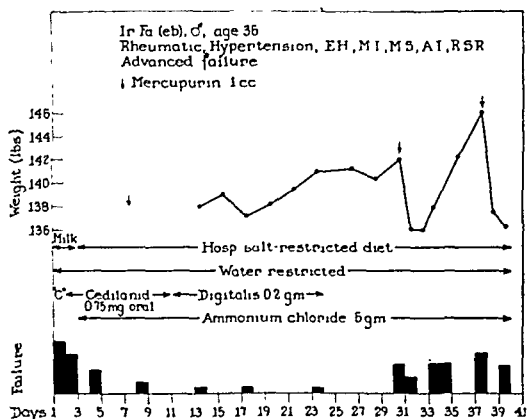


FIG. 14. Type of response of congestive failure to current methods of treatment.

FIG. 15. Type of response of congestive failure to current methods of treatment.

level of a constant moderate glycosuria). This now is the plan we advocate for the control of congestive failure, namely, the adjustment of the dose of the mercurial as well as the interval between doses in order to maintain a constant body weight after the optimum state has been established.

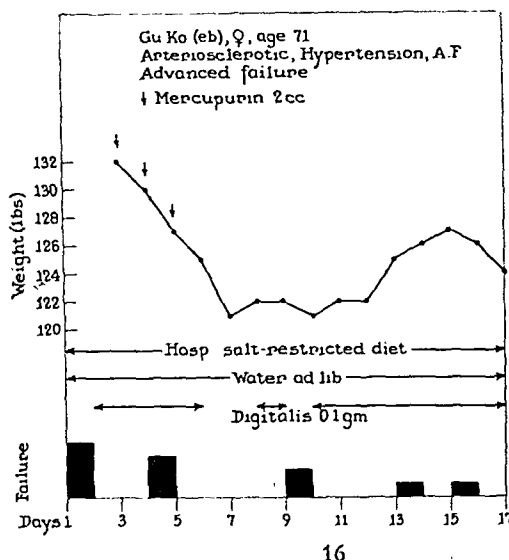


FIG. 16. Type of response of congestive failure to current methods of treatment.

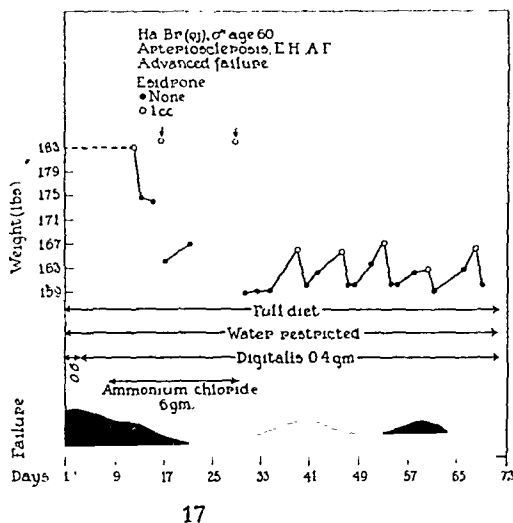


FIG. 17. Type of response of congestive failure to current methods of treatment.

Frequent injections often create a problem if a physician is necessary for all of them. We strongly urge, therefore, that a member of the family and sometimes the patient himself be instructed in the simple technic of an intramuscular injection after the physician has succeeded in establishing the proper maintenance program. The physician may then make periodic checks in order to determine any revision in the system which may become necessary.

Unpleasant Symptoms. An attempt was made to ascertain the nature of the unpleasant symptoms which might be ascribed to the proposed regimen in the 140 admissions so treated. There were such complaints as hunger, weakness, muscular cramps (six cases), nausea and vomiting (three cases), headache, dizziness, diarrhea (three cases) and constipation. It is difficult to be certain of the rôle of the treatment in causing any of these symptoms since these patients were all very ill and such symptoms are common in patients with advanced

stance of symptoms sufficiently disturbing to necessitate the interruption of treatment. There was no instance of the cerebral disturbances which have been described in relation to vigorous and excessive dehydration.^{33,34} At this point it is well to re-emphasize the fact that, while dehydration constitutes a conspicuous part of the plan of treatment, the details of its application take sufficient cognizance of the danger of excessive dehydration to insure against its occurrence.

Fatal Cases. Among the group of 133 patients described in the next section, who were treated by the proposed regimen, there were twelve deaths. The difficulties in determining the precise cause of death in patients with advanced congestive failure are well known. The numbers were not sufficient for a statistical comparison of causes of death in cases treated by this method with those treated by other methods. It seemed desirable, however, to present a brief summary of the course in these cases

to document our belief that the fatalities were of the same general variety known to occur in similar groups of patients treated by any method. They included active rheumatic carditis, renal failure, coronary thrombosis, cerebral vascular accidents, bronchopneumonia, a reaction to a bronchogram and unresponsive congestive failure.

COMPARISON OF RESULTS IN CONGESTIVE FAILURE TREATED BY THE CURRENT ROUTINE METHODS WITH THOSE BY THE PROPOSED METHOD

The records of 376 patients with congestive failure treated by routine methods in current use were examined. These methods (Figs. 12 to 17) varied considerably but all involved the use of digitalis, diuretics, attempts at salt restriction and attention to water intake. Various preparations of digitalis were employed and were given usually in divided doses, often taking several days for digitalization. Considerable dependence was placed on oral diuretics and mercurial diuretics were usually given at infrequent and irregular intervals. Frequently, diuretics were employed only after response to other measures had not proved sufficiently fruitful. Salt restriction was attempted by a variety of dietary adjustments; it was rarely systematic and was usually without adequate provisions for further reduction in the salt intake if the response proved inadequate. Water was commonly restricted. A chart of the body weight was not commonly used as the guide; the course was usually followed by changes in subjective symptoms and by inspection of gross and visible edema. The mercurial diuretics played little part in the plans for maintenance.

As seen in Table I, these patients had a total of 502 admissions. About three-fourths were admissions during the past ten years and about one-half in the past five years. The practice in four hospitals in New York is represented, one a large municipal hospital and three large voluntary hospitals. In the entire group of patients with congestive failure, an average of 23.6 days elapsed from the day of admission to discharge, varying

from nineteen to thirty days in the different hospitals.

The records were examined for all information relating to the type of heart disease, degree of failure, signs of improvement and degrees of recovery. The degrees of failure

TABLE I
DURATION OF HOSPITALIZATION OF PATIENTS WITH CONGESTIVE FAILURE TREATED BY THE ROUTINE METHODS IN CURRENT USE

Hospital	Years	No. Records Reviewed		Duration of Hospital Stay of All Admissions	
		Admissions	Patients	Average (days)	Range (days)
Bellevue Post-Graduate	1930-1947	179	121	19.0	2-137
	1935-1946	67	52	25.8	2- 82
Beth Israel	1938-1946	119	94	20.1	1- 59
Joint Dis-cases	1930-1946	137	109	30.1	1-101
Totals		502	376	23.6	1-137
	1930-1937	150 (29.9%)			
	1938-1947	352 (70.1%)			
	1942-1947	231 (46.2%)			

were classified into three groups: "moderate," those with shortness of breath on exertion, little or no orthopnea, pulmonary râles, liver edge not more than two fingers below the right costal margin and moderate pretibial edema; "advanced," those showing the foregoing signs but with the liver edge more than three fingers below the right costal margin and advanced edema of the legs; "extreme," those showing the foregoing signs including hydrothorax or ascites and/or edema up to and including the abdominal wall. In patients with predominantly so-called "left heart failure," the "moderate" included those with orthopnea, pulmonary râles and paroxysms of dyspnea; the "extreme" included those with pulmonary edema. The degrees of recovery were also classified into three groups: those

TABLE II

RESULTS OF TREATMENT BY CURRENT ROUTINES IN 376 PATIENTS WITH CONGESTIVE FAILURE
IN FOUR HOSPITALS

Etiology	No. Records Reviewed		Degree of Failure (Admissions)			Deaths among Patients	Degree of Recovery (Admissions)			Duration of Hospital Stay of All Admissions (days)	
	Admissions	Patients	Moderate	Advanced	Extreme		None or Very Slight	Moderate	Complete	Average	Range
			No. %	No. %	No. %		No. %	No. %	No. %		
Rheumatic.....	112	75	24 (21.4)	48 (42.9)	40 (35.7)	20 (26.7)	34 (30.4)	28 (25.0)	50 (44.6)	25.9	2-92
Arteriosclerotic.....	80	65	18 (22.5)	36 (45.0)	26 (32.5)	17 (26.2)	19 (23.8)	16 (20.0)	45 (56.3)	24.7	2-101
Hypertensive.....	287	218	76 (26.5)	129 (44.9)	82 (28.6)	50 (22.9)	77 (26.8)	72 (25.1)	138 (48.1)	22.8	1-137
Others.....	23	18	3 (13.0)	13 (56.5)	7 (30.4)	3 (16.7)	9 (39.1)	8 (34.8)	6 (26.1)	23.0	6-93
Totals.....	502	376	121 (24.1)	226 (45.0)	155 (30.9)	90 (23.9)	139 (27.7)	124 (24.7)	239 (47.6)	23.6	1-137

TABLE III

LENGTH OF TIME REQUIRED FOR RECOVERY IN 196 PATIENTS WITH CONGESTIVE FAILURE
TREATED BY THE ROUTINE METHODS IN CURRENT USE

Etiology	No. Records Reviewed		Degree of Failure (Admissions)			Time Required for "Cure" of Failure (days)		Duration of Hospital Stay of All Admissions (days)	
	Admissions	Patients	Moderate	Advanced	Extreme	Average	Range	Average	Range
			No. %	No. %	No. %				
Rheumatic.....	50	41	20 (40.0)	19 (38.0)	11 (22.0)	20.7	4-68	27.7	6-92
Arteriosclerotic.....	45	40	12 (26.7)	24 (53.3)	9 (20.0)	15.9	3-69	22.7	4-76
Hypertensive.....	138	108	60 (43.5)	51 (37.0)	27 (19.5)	12.7	3-33	20.8	3-133
Others.....	6	6	1 (16.7)	4 (66.7)	1 (16.7)	22.7	4-34	27.8	11-39
Totals.....	239	196	93 (38.9)	98 (41.0)	48 (20.1)	15.1	3-69	22.8	3-133

TABLE IV

RESULTS OF TREATMENT BY THE PROPOSED REGIMEN IN 133 PATIENTS WITH CONGESTIVE FAILURE

Etiology	No. Admissions	No. Patients	Degree of Failure (Admissions)			Deaths (Patients)	Degree of Recovery (Admissions)			Duration of Hospital Stay (days)	
			Moderate	Advanced	Extreme		None or Very Slight	Moderate	Complete	Average	Range
			No. %	No. %	No. %		No. %	No. %	No. %		
Rheumatic.....	31	28	0	15 (48.4)	16 (56.1)	2 (7.1)	1 (3.2)	0	30 (96.8)	16.2	4-34
Arteriosclerotic.....	44	42	4 (9.1)	16 (36.4)	24 (54.5)	2 (4.8)	0	6 (13.6)	38 (86.4)	12.5	5-30
Hypertensive.....	55	54	4 (7.3)	22 (40.0)	29 (52.7)	6 (11.1)	2 (3.6)	3 (5.5)	50 (90.9)	13.3	4-30
Others.....	10	9	0	2 (20.0)	8 (80.0)	2 (22.2)	0	2 (20.0)	8 (80.0)	16.0	5-30
Totals.....	140	133	8 (5.7)	55 (39.3)	77 (55.0)	12 (9.0)	3 (2.2)	11 (7.8)	126 (90.0)	13.7	4-34

in whom improvement was absent or negligible; "moderate," those in whom considerable relief of symptoms and edema had resulted although there still remained some gross edema and pulmonary râles; "complete," those in whom all symptoms of

plete." It took an average of about fifteen days, varying from about thirteen to twenty-three days, in the different types of heart disease.

Table iv summarizes the results with the proposed method of treatment in 133 pa-

TABLE V
LENGTH OF TIME REQUIRED FOR RECOVERY IN 119 PATIENTS WITH CONGESTIVE FAILURE
TREATED BY THE PROPOSED REGIMEN

Etiology	No. Admissions	No. Patients	Degree of Failure (Admissions)			Time Required for "Cure" of Failure (days)		Duration of Hospital Stay of All Admissions (days)	
			Moderate	Advanced	Extreme				
			No. %	No. %	No. %	Average	Range	Average	Range
Rheumatic	30	27	0	15 (50.0)	15 (50.0)	6.5	3-14	16.4	4-34
Arteriosclerotic	38	36	4 (10.5)	16 (42.1)	18 (47.4)	5.8	2-14	7.3	5-30
Hypertensive	50	49	4 (8.0)	20 (40.0)	26 (52.0)	6.5	3-18	12.7	4-30
Others	8	7	0	2 (25.0)	6 (75.0)	5.5	2- 8	14.5	5-30
Totals	126	119	8 (6.3)	53 (42.1)	65 (51.6)	6.2	2-18	12.1	4-34

failure and signs of edema had vanished although enlargement of the liver persisted, a change which is frequently permanent in patients with long standing congestive failure. These have been summarized in Table ii. All the common forms of heart disease are represented. About three-fourths of them were in at least "advanced" failure. Nearly one-fourth of them died and somewhat less than 50 per cent were discharged with recovery substantially complete.

In the case of those in whom recovery was "complete," a close approximation was made in arriving at the period from the time of admission to the disappearance of signs and symptoms. In comparing the two methods of treatment in the patients with "complete" recovery, the time it takes to bring it about has more meaning than the duration of hospital stay since the latter is often influenced by factors which have nothing to do with the treatment. Table iii summarizes the results of treatment with the current methods in 196 patients (239 admissions) in whom the recovery was "com-

plete." It took an average of about fifteen days, varying from about thirteen to twenty-three days, in the different types of heart disease.

Table v summarizes the results in 119 patients (126 admissions) treated by the proposed regimen in whom recovery was "complete." It took an average of about six days from the day of admission to the disappearance of signs and symptoms of failure.

It may be seen from Tables iii and v that for the two methods of treatment there were a similar number of admissions of hypertensive heart disease with failure in the most extreme degree in which recovery was "complete" (twenty-seven and twenty-six cases, respectively). These were examined for the time required for "recovery." The average for the current methods was 17.6 days (7-33); for the proposed method, 8 days (3-18).

Since, as seen in Table iii, rheumatic patients in failure tend to take longer to recover than hypertensive patients and since

the degree of failure might be expected to influence the time for recovery, it was necessary to ascertain whether or not the groups treated by the two methods were comparable with respect to these points. The characteristics of the two groups are assembled in

TABLE VI
CHARACTERISTICS OF THE PATIENTS WITH CONGESTIVE FAILURE USED IN THIS STUDY

Characteristics	Treated by Current Methods	Treated by the Proposed Regimen
Etiology (No. and per cent of patients)		
Rheumatic.....	75 (19.9%)	28 (21.1%)
Arteriosclerotic.....	65 (17.3%)	42 (32.3%)
Hypertensive.....	218 (58.0%)	54 (40.6%)
Others.....	18 (4.8%)	9 (6.9%)
Total.....	376	133
Males		
No. and per cent of patients.....	223 (59.3%)	89 (66.9%)
Females		
No. and per cent of patients.....	153 (40.7%)	44 (33.1%)
Age		
Average.....	50.8	57.0
Range.....	7-81	20-83
Degree of failure (No. and per cent of admissions)		
Moderate.....	121 (24.1%)	8 (5.7%)
Advanced.....	226 (45.0%)	55 (39.3%)
Extreme.....	155 (30.9%)	77 (55.0%)
Total.....	502	140

Table vi. It may be noted that they are substantially similar with respect to etiology, sex, and age. In regard to the severity of the failure, the group treated by the proposed method had a higher incidence of the more severe grades of failure.

It is well known that patients with predominantly so-called "left heart failure" often become free of symptoms rapidly after being put at rest, much more so than in those who also have a large element of so-called "right heart failure" with massive edema and ascites. In Table vii, the two groups are compared with regard to the different types of congestive failure. It may be noted that the two groups are practically

identical with respect to the representation of the two types of congestive failure.

The essential results by the two methods of treatment are summarized in Table viii. The term "maximum results" used in this table has a fairly precise meaning for those

TABLE VII
LENGTH OF TIME REQUIRED FOR RECOVERY IN DIFFERENT TYPES OF CONGESTIVE FAILURE

	Treated by Current Routine Methods	Treated by the Proposed Regimen
No. patients.....	196	119
No. admissions.....	239	126
"Left cases" (predominantly "left failure").....	49 (20.5%)	23 (18.3%)
(No. and per cent admissions)		
"Right cases" ("right failure" with varying degrees of "left failure")...	190 (79.5%)	103 (81.7%)
(No. and per cent admissions)		
Days to recovery in "left cases".....	10.8	4.3
Days to recovery in "right cases".....	16.2	6.6
No. and per cent "left cases" in the etiologic groups		
Rheumatic.....	15 (30%)	3 (10%)
Arteriosclerotic.....	8 (17.8%)	8 (21.1%)
Hypertensive.....	25 (18.1%)	9 (18%)
Other.....	1 (16.7%)	3 (27.5%)
No. and per cent "right cases" in the etiologic groups		
Rheumatic.....	35 (70%)	27 (90%)
Arteriosclerotic.....	37 (82.2%)	30 (78.9%)
Hypertensive.....	113 (81.9%)	41 (82%)
Other.....	5 (83.3%)	5 (82.5%)

patients treated by the proposed method. It was taken as the point at which signs and symptoms of failure subsided and the body weight reached a resistant level or the point at which the course of treatment seemed to produce no further improvement. However, in many of the patients treated by the prevailing methods, the decision concerning "maximum improvement" presented considerable difficulty, since their course so often represented an endless succession of advances and regressions which, after the

patient had lingered in bed for a period of 30 or 40 days, seemed to have been terminated quite arbitrarily by a sense of futility. (Figs. 13, 14 and 17.) It may be seen that in two substantially similar groups of patients, the results with the current methods of

COMMENT

This study has placed agents for dehydration (the mercurial diuretic and salt restriction) in the first rank among measures effective in the control of congestive failure. How does this accord with the prevailing views regarding the mechanism of congestive failure?

There have been many important reviews of the mechanism of congestive failure. A very informative analysis of the literature was recently published by Ellis.³⁵ There is now considerable resistance to the idea that the symptoms of congestive failure are the direct mechanical consequence of a diminished circulation.^{36,37} It is clear that the term congestive failure, as applied to a clinical state, may embrace different physiologic abnormalities in different cases and in different stages.

Ellis restated the prevailing view that weakness of the contractile force of the heart muscle initiates the train of events although he points out that secondary factors may outweigh the importance of the initial cause. The formulation of congestive failure on the basis of primary muscle weakness has buttressed the common practice of placing digitalis first among the remedies for congestive failure because of its power to increase the contractile force of the failing heart muscle.³⁸ This notion has become so firmly fixed that it has tended to obscure the magnitude of the clinical problem of congestive failure in which digitalis seems to exercise little or no beneficial influence.

The chief types of cases in which the effect of digitalis is negligible or limited might be mentioned: There is the congestive failure in the course of active rheumatic carditis in which little tendency to control results from digitalis, such patients often advancing to pronounced edema while fully digitalized. There are the cases of mitral stenosis in which the sole symptoms and signs of congestive failure are shortness of breath, pulmonary râles or attacks of pulmonary edema. Digitalis is usually of little or no benefit in these. There is the large group of

TABLE VIII
RESULTS IN CONGESTIVE FAILURE TREATED BY CURRENT METHODS COMPARED WITH THOSE BY THE PROPOSED REGIMEN

	Treated by the Current Methods	Treated by the Proposed Regimen
No. admissions . . .	502	140
No. patients	376	133
Males	59 3%	66 9%
Females	40 7%	33 1%
Average age (and range) . .	50 8 (7-81) yr.	57 0 (20-83) yr.
Etiology (per cent patients)		
Rheumatic	19 9%	21 1%
Arteriosclerotic	17 3%	32 3%
Hypertensive	58 0%	40 6%
Other	4 8%	6 9%
Degree of congestive failure (Per cent admissions)		
Moderate	24 1%	5 7%
Advanced	45 0%	39 3%
Extreme	30 9%	55 0%
Deaths (per cent patients) . .	23 9%	9 0%
Degree of recovery (Per cent admissions)		
None or slight	27 7%	2 2%
Moderate	24 7%	7 8%
Complete	47 6%	90 0%
Weight loss in admissions with complete recovery (average and range)	*16.4 (2-41) lb.	*15 6 (2-55) lb.
Duration of hospital stay . . . (All admissions—average and range)	23 6 (1-137) days	13 7 (4-34) days
Average time to maximum improvement	†19.6 days	†6 4 days
Time to recovery (In those who recovered completely—average and range)	15.1 (3-69) days	6 2 (2-18) days

* Sufficient weighings to be used as a guide were made in only 95 of the 239, and 122 of the 126 admissions, with complete recovery.

† Based on 419 admissions in the case of the current methods, and 134 in the case of the proposed method. They include deaths (seven and six cases, respectively, in the two groups) in which improvement of failure resulted although patients subsequently died of one or another cause.

treatment show 47.6 per cent "complete" recoveries, 23.9 per cent deaths, an average of 19.6 days for the maximum results yielded by the particular treatment in all admissions and an average of 15.1 days required for "complete" recovery; while the results with the proposed method of treatment show 90 per cent "complete" recoveries, 9 per cent deaths, an average of 6.4 days for maximum results obtained in all admissions and an average of 6.2 days required for "complete" recovery.

patients with arteriosclerotic and hypertensive disease subject to dyspnea on exertion, orthopnea or attacks of pulmonary edema without signs of systemic congestion of "right heart failure." A very considerable proportion of these show little or no improvement with the digitalis glycosides. As a group, patients with difficulty predominantly on the pulmonary side ("left heart failure") do not respond nearly as well as those with the chief trouble in the systemic circuit ("right heart failure"). There is the long-standing controversy concerning the value of digitalis in congestive failure with sinus rhythm. Sir Thomas Lewis³⁹ considered it of importance only in auricular fibrillation. Luten⁴⁰ and Marvin⁴¹ were among those who early showed it to be of substantial value also in cases with sinus rhythm. This has been amply confirmed, but the fact remains that as a group, those with sinus rhythm do not respond to digitalis nearly as well as those with auricular fibrillation; and the number of patients with congestive failure and sinus rhythm in whom digitalis exerts no conspicuous effect is quite impressive. Then there is the group of cases of congestive failure, long effectively maintained by digitalis alone, who, in advanced stages, also require the diuretic to enable them to carry on.

The point that must be stressed is the fact that diuretic agents are not only helpful in accelerating recovery in cases in which digitalis alone may suffice after a more protracted course but that these agents alone, when effectively applied, control the congestive failure in a large proportion of those types of cases in which digitalis produces little or no benefits. We have numbers of patients with mitral stenosis and evidence of advanced pulmonary congestion (pulmonary râles, fluoroscopic signs) without systemic congestion in whom dyspnea, orthopnea and attacks of pulmonary edema are entirely uninfluenced by digitalis but in whom these symptoms and signs are brought under a high degree of control by an effective system of dehydration which maintains the patient in the state we have described as the "dry weight." The same is true, per-

haps to an even more striking degree, in patients with hypertensive disease. Many of these patients, even when fully digitalized, suffer with frequent attacks of nocturnal dyspnea or pulmonary edema; these often vanish on a system of diuretic measures which effectively establish and maintain the "dry-weight." In children with congestive failure resulting from active carditis, the edema often has a renal distribution. It has been pointed out in the literature⁴² that the diuretics are very effective in these and that in many of such cases in which digitalis is of little or no benefit the symptoms and the edema may be brought under control by the use of a potent diuretic.⁴³

It may be well to mention at this point a common source of misunderstanding. Physicians are accustomed to apply the term congestive failure only to those patients with pitting edema of the legs or enlargement of the liver or pulmonary râles. We have encountered resistance to the idea of using diuretic agents in the absence of these signs on the grounds that there was no evidence of congestive failure. It should be remembered that the extracellular fluid may increase to 50 per cent above normal before pitting of the legs occurs⁴⁴ and that the presence of pulmonary râles depends on the location of the fluid in the lungs;⁴⁵ there are râles if the edema fluid is intra-alveolar but there may be none if the fluid is interstitial. Many patients in congestive failure with an extreme sense of suffocation do not show any pulmonary râles. A typical case of this kind is shown in Figure 18. The patient, a physician, was sixty-one years old. He had hypertensive and arteriosclerotic heart disease for many years and had developed massive enlargement of the heart. Two years ago, he began to suffer with shortness of breath on exertion. This increased progressively until orthopnea and paroxysmal dyspnea appeared. In the past eight months, he was completely incapacitated; he was barely able to lie down without a sense of suffocation; he was subject to paroxysms of dyspnea even while sitting in bed or in a chair. A course of treatment in the hospital

failed to bring about any improvement. This treatment consisted of intensive digitalization, several doses of papaverine daily and sedation. A dose of $\frac{1}{4}$ gr. of morphine resulted in profound depression with Cheyne-Stokes respiration. An intravenous

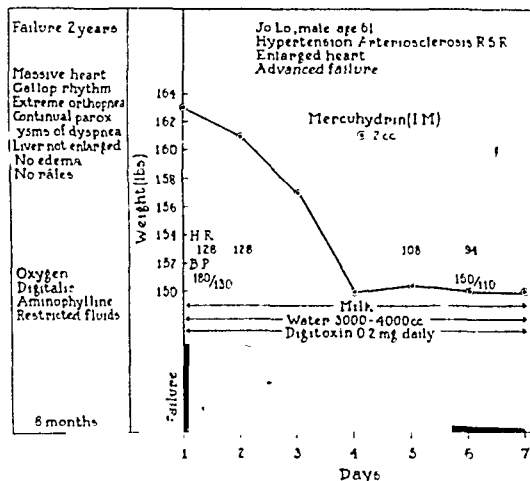


FIG. 18. Typical response of congestive failure to the proposed regimen. Note the fact that extreme respiratory distress existed and was promptly relieved with the loss of 10 pounds of fluid in a patient in whom there were none of the usual signs of congestive failure (no râles, no edema of the legs and no enlargement of the liver).

injection of aminophylline was used once or twice a day since it seemed to relieve the respiratory distress for a period of four or five hours. His physician labeled his diet "salt-free" but it turned out to be a regular diet in which salt was used freely in the cooking; however, salt was withheld from the tray. Emphasis was placed on the restriction of water and the patient frequently took pains to avoid an intake of more than 500 cc. a day. Matters went from bad to worse and at the time the revised treatment was applied all hope for recovery had been abandoned. The patient was readmitted to the hospital. The blood urea nitrogen at this time was 27 mg. The patient was placed on a diet consisting of six glasses of milk daily and a daily water intake of between 3,000 and 4,000 cc. A long discussion in more than one session was necessary to shake his conviction that so much water would do harm. In addition, he received a daily intramuscular injection of 2 cc. of mercuhydrin. Within four days, the patient lost a total of 10

pounds of body weight; the blood urea nitrogen was 26 mg. at this time. The relief of symptoms was dramatic; dyspnea and orthopnea vanished and on the sixth day the patient was discharged from the hospital with a maintenance system of treatment to be carried on at home. It should be re-emphasized that the need for a course of dehydration had not been suspected by his physician because the patient presented none of the usual signs of edema; the lungs were clear; there were no pulmonary râles; there was no pitting edema of the legs and there was no enlargement of the liver.

If it is a fact that heart muscle weakness initiates the train of events in congestive failure, the absence of therapeutic response to digitalis in so many suggests the possibility that there may be different types of muscular failure, some of which are and some are not reversed by digitalis. In our studies with the papillary muscle,⁴⁶ we encountered some preparations in which the glycosides did not succeed in enhancing the systolic force. The conditions determining a positive response are unknown although it was observed that failures were more frequent with the muscle in serum than in Ringer's solution.

It may be noted, however, that what initiates the train of events may be of only limited importance from the practical standpoint. The case of acute coronary thrombosis may serve to illustrate the point. The initial injury to the contractile power of the heart is promptly followed by a profound slowing of the circulation and fall of the systemic pressure, a state of peripheral circulatory shock. It begins as an acute failure of the heart but shock soon takes over, and the therapeutic problem is often best met by the treatment of the shock, not that of the primary muscle failure of the heart which initiated it.

In a broader sense, heart muscle weakness can be viewed only as one of the links in a complex chain of causation; there are antecedent factors in heart disease, possibly chemical, which give rise to the muscle weakness and the latter in turn (as well as other factors) may give rise to a disturbance

which is the immediate cause of the signs and symptoms of the clinical state, known as congestive failure. The evidence is becoming increasingly convincing that the immediate cause is a disorder in salt and water metabolism leading to tissue hyperhydration. The disturbance in electrolyte balance in heart disease, the existence of which was noted nearly fifty years ago,⁴⁷ has received special attention in recent years. Futcher and Schroeder²⁵ found that patients with chronic heart disease (recovering from congestive failure) have a markedly diminished capacity to excrete salt, 30 per cent of the normal or less, and indicated that it may be due to an increased renal reabsorption of salt. The studies of Warren and Stead⁴⁸ and of Merrill⁴⁹ have emphasized the renal factor in the retention of salt in patients with congestive failure. Further light has been thrown on this subject by the very interesting work of Reaser and Burch⁵⁰ with radioactive sodium. Not only is salt retained by patients in congestive failure but excessive salt administration may precipitate the typical signs and symptoms of congestive failure in patients with heart disease² as well as in some without heart disease.⁵¹ It is also noteworthy that hypertension, a condition which most commonly gives rise to congestive failure, involves a disturbance in the behavior of salt, a resistance to salt loss when the patients are placed on a highly restricted salt intake⁵² and marked lowering of blood pressure in some of these patients when they are placed on a diet of extremely low salt content.⁵³

From the theoretical standpoint, the clinical syndrome of congestive failure may be defined in terms of a disturbance occurring either at the level of heart muscle contraction or at the level of the electrolyte imbalance or a disturbance at any other level which may represent a link in the chain of causes. However, from the practical standpoint it would seem appropriate to define the clinical syndrome in terms of the link in the chain of causation which is most accessible to attack and at which point it can be most regularly interrupted. Accord-

ingly, congestive failure may be formulated as a clinical state involving a disturbance in salt and water metabolism leading to tissue hyperhydration, occurring most commonly in chronic heart disease and resulting usually from a chronic circulatory disorder in the pulmonary or systemic circuit.

The foregoing observations, we believe, lend support to the position that the sequence employed in the most common practice of trying digitalis first and then adding a diuretic, if necessary, is in need of revision. In the concept of treatment, the indications are that the order should be reversed; an effective technic for dehydration with salt restriction, free supply of water and a potent diuretic become the base of the system; digitalization becomes an auxiliary or accessory measure, without value in many but of some use in others, and essential in a certain group, especially those with auricular fibrillation.⁵⁴ From the standpoint of results, this seems to be a more fruitful approach; there is indication that the incidence of improvement in congestive failure may be much higher from an effective system of dehydration alone than from digitalis alone.⁵⁰ Since there is no satisfactory way of distinguishing the two types of cases and since there is considerable overlapping, that is, patients who do better when receiving both measures, it is advocated for the present that both be used simultaneously in a routine manner until proof appears in a particular case that it is feasible to dispense with one or the other.

SUMMARY AND CONCLUSIONS

In this report a method is described for the routine treatment of congestive failure which brings the problem of congestive failure under a degree of control which has not been secured with any of the methods in general routine use.

It is pointed out that heart muscle weakness represents only one of the links in a complex chain of causation of the clinical state of congestive failure and that another link, namely, that of a metabolic disturbance involving salt and water retention, constitutes a more important one from the

therapeutic standpoint. In this system diuretic agents are the primary factors and digitalis plays a secondary rôle.

The proposed method is applicable not only to patients with advanced failure with pitting edema, enlarged liver, pulmonary râles and effusions but to the large group of cardiac patients with only shortness of breath on exertion, orthopnea, attacks of cardiac asthma, or pulmonary edema, and to a proportion of patients in whom the presenting symptoms of failure are paroxysms of disordered rhythm or attacks of cardiac pain. It provides relief for the large group of cardiac patients in whom digitalis is of little or no benefit.

The regimen is easily applied both in the hospital and in the home. It requires a minimum of nursing and medical supervision. It involves five cardinal factors: the simultaneous use of the mercurial diuretics, salt restriction, abundant water, digitoxin and the charting of the course by a record of the body weight. The measures are arranged in a system which provides the most effective results most quickly in the largest number. The secret of success lies in the way these measures are combined and applied.

It provides not only for abolishing the signs and symptoms of failure but for the maintenance of the gains. The same five cardinal factors used in abolishing an attack are also employed in the system for maintenance to prevent the recurrence of congestive failure.

The present study, comparing the results in 502 admissions for congestive failure (representing a cross section of the current practice in New York City) with the results in 140 similar admissions treated by the proposed system, shows that the symptoms and signs of congestive failure subside in about 90 per cent of hospital admissions, when this system is employed routinely, as against about 50 per cent with the current methods in common use; and the duration of required hospital stay is reduced to about one-third of the time necessary to bring about similar results by the current methods of treatment. The provisions for main-

tenance greatly reduce the high incidence of multiple hospital admissions occurring with the prevailing treatment. Broadly speaking, only two types of results are obtained with the proposed method, namely, a few failures and the rest complete recoveries. A third class, representing about one-third of the patients treated by other routines, namely, those with only moderate improvement, has practically vanished.

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CASE REPORTS OF PATIENTS WHO WERE TREATED BY THE PROPOSED REGIMEN AND WHO DIED

CASE 1. Patient Ri. Ab., a male, thirty-six years old, had rheumatic heart disease with enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, tricuspid insufficiency, normal sinus rhythm, advanced congestive failure and active rheumatic carditis. He was admitted with a temperature of 102°F. The routine regimen was applied. Symptoms and

signs of failure subsided after six daily doses of 2 cc. mercurhydrin; there was a loss of 11 pounds. The blood N.P.N. values during this week were 37, 25 and 30 mg. per 100 cc. In the next ten days, he received a total of four similar injections. On the thirteenth day of admission, he developed paroxysms of auricular fibrillation with heart rates as high as 160 a minute, with cough, blood-tinged sputum and severe dyspnea. The temperature during this time was as high as 101.4°F. Attempts to control the symptoms and fibrillation by means of oxygen and quinidine were unsuccessful and the patient was found dead in the early hours of the morning of the seventeenth day.

Comment: Death was probably due to active rheumatic carditis, after satisfactory initial response to therapy.

CASE II. Patient He. Ok., a male, forty years old, had syphilis, rheumatic heart disease with enlarged heart, aortic insufficiency, mitral insufficiency, normal sinus rhythm, extreme congestive failure and possible active rheumatic carditis. The patient was nearly moribund on admission. The routine regimen was applied. The urine output was 500 cc. on day of admission, and continued essentially unchanged during treatment which included 2 cc. mercurhydrin every twelve hours. There was no response and the patient expired on the fourth day.

Comment: Death was due to congestive failure with possible active rheumatic carditis, without response to therapy.

CASE III. Patient Le. Wa., a male, sixty years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, advanced congestive failure and pulmonary emphysema. He had received three doses of a mercurial weekly for six months. The routine regimen was applied. Symptoms of failure disappeared after five daily doses of 2 cc. of the mercurial; there was a loss of 9 pounds. No more doses of the mercurial were given. On the seventh day, the patient developed abdominal cramps, diarrhea and vomiting and symptoms progressed to coma, collapse and death on the fourteenth day. There was a clinical diagnosis of uremia. Laboratory data on the eleventh day: blood proteins 5.7 per cent; N.P.N. 129 mg. per 100 cc.; CO₂ combining power 22 vols. per cent. Postmortem report: primary contracted kidney; no lesions in gastrointestinal tract to account for symptoms; opinion of pathologist: kidney lesion not due to mercury.

Comment: Death was due to uremia of primary contracted kidney after satisfactory initial response to therapy.

CASE IV. Patient Ad. Ba., a female, sixty-one years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, auricular fibrillation, extreme congestive failure, extreme emaciation (weight 114 pounds., hemoglobin 8.5 Gm., red blood cells 2.9 million) and the specific gravity of urine was fixed between 1006 and 1010. The routine regimen was applied. Symptoms of failure subsided after six daily doses of 2 cc. mercurhydrin; there was a loss of 22 pounds. In the next eleven days 4 doses of 1 cc. mercurhydrin were administered. Being a case treated on another service, a daily dose of 6 Gm. ammonium chloride was used throughout the course, and water intake was not supervised and was low. On the fourteenth day, the patient developed drowsiness. Although free of congestive failure, her condition deteriorated in spite of intravenous infusions and she died on the seventeenth day. The blood N.P.N. on admission was 67 mg. per 100 cc., 75 mg. on the seventh day, and 85 mg. on the thirteenth day. Post-mortem report: primary contracted kidney and cerebral edema.

Comment: Death occurred because of renal failure due to primary contracted kidney after satisfactory initial response to therapy.

CASE V. Patient Sa. Br., a female, sixty-three years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure, hypertensive encephalopathy and was nearly moribund. The routine regimen was applied; there were fourteen daily doses of 2 cc. mercurhydrin. The gross edema which extended to the breasts showed some regression but total improvement was slight. A confusional state persisted and the patient died on the fourteenth day.

Comment: Death caused by advanced congestive failure and hypertensive encephalopathy which showed only slight response to therapy.

CASE VI. Patient Ab. Ax., a male, sixty-six years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure and possible acute coronary thrombosis. The routine regimen was applied. He received fourteen daily doses of 2 cc. mercurhydrin with slight response and thoracic pain persisted. Being a case treated on another service, a daily dose of 6 Gm. ammo-

nium chloride was used throughout the course, and water intake was not supervised and was low. The patient died suddenly on the morning of the fifteenth day. Blood N.P.N. on the thirteenth day was 63 mg. per 100 cc.

Comment: Death was probably due to acute coronary thrombosis or pulmonary infarction without response to therapy.

CASE VII. Patient Da. Ab., a male, sixty-nine years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure, diabetes, pulmonary emphysema and had suffered a cerebral vascular accident one year previously. The routine regimen was applied. Symptoms of failure subsided after five daily doses of 2 cc. mercurhydrin; there was a loss of 7.5 pounds. On the fifth day, he died suddenly while talking to another patient. Blood N.P.N. on the fifth day was 47 mg. per 100 cc.

Comment: Death was probably due to cerebral vascular accident, after satisfactory initial response to therapy.

CASE VIII. Patient Le. Sc., a female, eighty years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, auricular fibrillation, extreme congestive failure, parkinsonism and senile dementia (disoriented). The routine regimen was applied. Symptoms of failure diminished moderately after six doses of 2 cc. mercurhydrin in the first seven days; there was a loss of 15 pounds. No more doses of the mercurial were given. The patient was disoriented throughout the course and on the seventh day developed drowsiness and Cheyne-Stokes respiration after 2 Gm. chloral hydrate. There was a clinical diagnosis of cerebral vascular accident. The patient became stuporous; her temperature rose as high as 104°F. (possible pneumonia) and she expired on the ninth day. Blood N.P.N. on admission was 37 mg. per 100 cc., 64 mg. on the fourth day, 34 mg. on the seventh day and 80 mg. on the eighth day.

Comment: Death was probably due to cerebral vascular accident with terminal pneumonia in an aged person with advanced arteriosclerotic cerebral changes after moderate initial response to therapy.

CASE IX. Patient Sa. Ro., a male, sixty-three years old, had hypertensive and arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, extreme congestive failure and morphine addiction. The routine regimen was applied and he received twenty-one daily

doses of 1 cc. mercurhydrin. Improvement was slight (lost 4.5 pounds in first three days). His course was progressively downward and he expired with symptoms of extreme failure and coma on the twenty-first day. Post mortem report: extensive pathologic changes, purulent pericarditis, consolidation of lower lobes of both lungs; advanced ulcerative and calcified lesions of the aorta, small contracted kidneys and massive cirrhotic liver.

Comment: Death was due to extreme congestive failure and bronchopneumonia with slight initial response to therapy.

CASE X. Patient Sa. Fe., a female, seventy years old, had arteriosclerotic heart disease with enlarged heart, normal sinus rhythm, coronary thrombosis, extreme congestive failure and diabetes. The routine regimen was applied. Symptoms of failure subsided after eleven daily doses of 2 cc. mercurhydrin; there was a loss of 34 pounds. On the thirteenth day, the patient developed a severe attack of pain in the chest and left shoulder and died during sleep.

Comment: Death was probably due to acute coronary thrombosis or pulmonary infarction after complete recovery from congestive failure.

CASE XI. Patient Wa. Mc., a male, forty-three years old, had bronchial asthma, pulmonary emphysema, cor pulmonale, bronchiectasis, normal sinus rhythm and extreme congestive failure. The routine regimen was applied. Symptoms of failure subsided after seven daily doses of 2 cc. mercurhydrin; there was a loss of 30 pounds. In the next ten days, six doses of 2 cc. mercurhydrin were administered. Because of the severe respiratory symptoms, the patient received almost daily doses of aminophylline and remained in the hospital for bronchogram which was performed on the thirteenth day. On the following day, dyspnea became intense, coma developed and the patient died of respiratory failure on the sixteenth day although clear of congestive failure. Blood N.P.N. ranged from 21 to 33 mg. per 100 cc. Postmortem report: cor pulmonale, bilateral bronchiectasis with cavities, edema of brain and normal kidneys.

Comment: Death caused probably by reaction to bronchogram after satisfactory initial response to therapy.

CASE XII. Patient Ma. Be., a male, sixty-one years old, had pulmonary fibrosis and emphysema, cor pulmonale, normal sinus rhythm, extreme congestive failure (intense cyanosis with periodic lapses into coma). The routine regimen

was applied. Considerable relief of symptoms occurred after seven doses of 2 cc. mercurhydrin in the first eight days and 2 cc. every twelve hours during the subsequent eight days; there was a loss of 28 pounds. There were many temporary changes in cardiac rhythm during the course, paroxysms of bigeminy and auricular fibrillation. Blood N.P.N. on admission was 50 mg. per 100 cc., 74 mg. on the fifth day, 80 mg. on the sixth day, 53 mg. on the eighth day, 48 mg. on the tenth day, 38 mg. on the twelfth day, 49 mg. on the thirteenth day and 39 mg. on the fifteenth day. In the early hours of the seventeenth day the patient was found dead in bed (seen awake, alert, and without complaints 30 minutes previously).

Comment: Death possibly was due to cerebral vascular accident after marked initial response to therapy.

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Oral Administration of Mercupurin Tablets in Ambulatory Patients with Chronic Congestive Heart Failure*

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THERE are many patients with chronic congestive heart failure who, in spite of adequate treatment with the usual drugs, dietary control and parenteral mercurial diuretics, do not do well and constitute an important therapeutic problem. Because the immediate response to mercurial injections in this group of patients is usually satisfactory, it seemed that the problem might be approached by the administration of mercurial diuretics in such a manner as to produce a more constant diuresis. Since daily injections of mercurials are not practical over a long period of time, we attempted to achieve this result by the oral administration of mercurial diuretics. The published reports on this method of treatment were not promising¹ except for those by Batterman et al.,^{2,3} who suggested that the drug might be a useful adjunct in the treatment of chronic congestive heart failure.

The idea of giving mercupurin constantly to control chronic congestive failure or possibly to prevent recurrence, although not commonly practiced, is feasible and has been suggested by Gold;⁴ oral administration of mercupurin tablets† instead

† Each tablet contains 120 mg. of mercupurin, which is equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline, whereas 1 cc. of the parenteral solution contains 135 mg. of mercupurin. Mercupurin tablets were supplied by Campbell Products, Inc., New York, N. Y.

of injections seemed more desirable and worthy of trial.

PLAN OF TREATMENT AND SELECTION OF PATIENTS

Patients were selected who had been under our own observation for a long period of time and who demonstrated chronic or recurrent congestive heart failure in spite of adequate treatment, including repeated injections of mercurial diuretics. Patients with impaired renal function were excluded. Our initial method of oral mercury treatment was experimental and included varying doses given in a variety of ways, as indicated below. Our aim was to find for each patient a method of administration and dosage of the mercupurin tablets which would relieve the signs and symptoms of congestive heart failure with minimal or no toxic reactions.

The preliminary methods of dosage and administration used were: (1) One tablet two or three times a day, or two tablets before breakfast for five consecutive days each week; (2) one to three tablets before breakfast every other day, or one to three tablets at bedtime every other evening; (3) five tablets before breakfast once or twice a week and (4) one to three tablets every morning before breakfast, or one tablet two or three times each day.

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The eleven patients investigated were ambulatory, had signs of gross congestive failure and were seen in the Cardiac Clinic at frequent intervals. In addition to oral mercupurin all patients were receiving digitalis and were on a low salt diet. All

TABLE I
PLAN OF ADMINISTRATION AND DOSAGE OF MERCUPURIN TABLETS

	Cases	Dosage
Daily	II, V and VIII VI	Three tablets each morning before breakfast One tablet three times a day
Five consecutive days each week	I and IV VII	One tablet three times a day Two tablets every morning before breakfast
Every other morning before breakfast	IX and X	Three tablets
Every other evening at bedtime	XI III	Three tablets Two tablets

but one of the patients received ammonium chloride continuously.

As a result of our preliminary investigations the plan of treatment finally evolved consisted of hospitalizing those patients with signs of gross congestive heart failure who did not respond to oral therapy and of re-instituting oral therapy after all signs of failure disappeared. The plan of administration and dosage of mercupurin tablets found most effective was quite variable. (Table I.) No one of these plans in practice has proven uniformly superior. In treating a patient who tends to gain weight on an optimum regimen including acidifying salts, it has been our practice to initiate one of the four plans of treatment and change or modify it if toxic symptoms develop or if the symptoms and signs of congestive heart failure are not relieved. As soon as the most

suitable plan was established, the patient followed it continuously.

When symptoms or signs of failure recurred under certain conditions (respiratory infections, paroxysmal rapid heart action, discontinuance of the tablets), one or two

TABLE II
DURATION OF ORAL MERCUPURIN MEDICATION

Cases	Duration in Months
I and IV	27
III	25
VII	20
IX	14
XI	12
VI	10
V	8
X	7
II	4½
VIII	3

doses of mercurial diuretic were given parenterally at weekly intervals, with continuance of the oral tablets.

At each visit the patient was given a supply of tablets sufficient to enable him to follow the prescribed plan of administration and dosage and was instructed not to deviate from this plan. At each visit the patient was questioned and examined for evidence of congestive heart failure and mercurialism. The patient's weight was recorded and the urine examined. In patients who showed albuminuria before the institution of the tablet regimen the blood non-protein nitrogen was determined at each visit.

RESULTS

The results were uniformly excellent and parenteral injections of mercurials were not necessary except as noted below. The patients have taken the mercupurin tablets for three to twenty-seven months (Table II).

Within one or two weeks after the institution of oral therapy, a loss of weight of 5 to 25 pounds was observed, following which the weight remained stationary.

The efficacy of treatment with mercupurin tablets was further shown by the effect of discontinuance of the treatment.

Cases I, IV, VII, IX and X developed signs and symptoms of congestive heart failure with increases in weight within three days to one week after the mercupurin tablets were omitted. With resumption of the mercupurin tablets and one or two doses of parenterally administered mercupurin, these patients became free of congestive failure and their weights returned to the previous stationary levels. In spite of the uninterrupted ingestion of the tablets, Cases I, IV and VI developed recurrence of signs and symptoms of congestive heart failure during respiratory infections. Case I required parenteral mercupurin while the oral tablets were continued; Case IV was hospitalized and Case VI regained his previous cardiac status with continuance of the oral mercupurin without the drug administered parenterally. Case I developed signs and symptoms of congestive failure after an episode of paroxysmal rapid heart action. With continued use of the mercupurin tablets and one parenteral dose of mercupurin she regained her former status.

Toxic Manifestations. Five patients (Cases IV, V, VIII, IX and X) on various dosage schedules have been free of toxic manifestations after taking the oral mercupurin from seven to twenty-seven months. Six others had toxic manifestations of one or several types.

Soreness of the abdomen without bowel symptoms was present in Case I on the days she took the tablets for a period of two months, one year after she began taking them. This complaint disappeared in spite of continued ingestion of the tablets. Anorexia and slight nausea, on the days Case XI ingested the tablets, developed five months after she began to take them and recurred for four months. These complaints disappeared after the time of administration was changed to the evening at bedtime. Abdominal cramps with or without diarrhea developed in Cases II, III, VI and VII. In

Case II the cramps developed during the first week of ingestion of the tablets, disappeared in spite of the continued ingestion of the drug and failed to recur when the dosage of the drug was increased. In Case III two months after the oral tablet regimen was begun, increase of the dosage was accompanied by abdominal cramps and two to three bowel movements on the day following the ingestion of the tablets. Reduction of the dosage relieved the abdominal complaints. Case VI developed bloody stools and abdominal cramps for one day, three weeks after the ingestion of the tablets was begun. The tablets were omitted for several days with disappearance of the complaints. Two and three months after beginning the tablets he suffered with bouts of diarrhea and cramps, each lasting one day. These complaints disappeared in spite of the continued ingestion of the tablets. Eight months after beginning the tablets he suffered with diarrhea on three occasions, each lasting one day. These complaints disappeared although the tablets were continued. Case VII complained of abdominal cramps with one bowel movement a day during the second week after the ingestion of mercupurin tablets was begun. These complaints disappeared in spite of the continued use of the tablets. In the third week he developed anorexia, pain and itchiness of the gums. The tablets were then omitted for three weeks with disappearance of the complaints. Four and one-half months after the tablets were resumed he again complained of pain in his gums and teeth. The tablets were then omitted for six weeks, during which time the gums became normal except for residual pyorrhea. The tablets were then resumed for one year without recurrence of the gastrointestinal or gum difficulties.

Five patients (Cases I, II, III, IV and IX) showed no albumin in the urine throughout the study period. Six patients (Cases V, VI, VII, VIII, X and XI) had albuminuria before

the study was undertaken and continued to show varying amounts of albuminuria throughout the period of the study. Three patients (Cases I, II and III) with toxic gastrointestinal manifestations showed no albuminuria, while three patients (Cases VI, VII and XI) with albuminuria before and during the study developed toxic gastrointestinal symptoms and showed no increase in albuminuria.

Case II developed severe acute mercurialism after he had received oral mercupurin therapy for four and one-half months, during which time he was free of signs and symptoms of congestive heart failure and showed repeatedly negative urines. One week before the symptoms of mercurialism appeared a urine examination showed 4 plus albumin. Unfortunately, this finding was not reported promptly and the drug was continued an additional week at the end of which time the patient developed the picture of acute mercurialism with shock, renal insufficiency, hypochloremia, hypoproteinemia, anasarca and hypercholesterolemia. Symptoms of congestive heart failure were absent. Repeated attempts to raise the colloid osmotic pressure of the blood were unsuccessful and the patient expired one month after the onset of the acute symptoms.

COMMENTS

As pointed out by Batterman et al.,² although the immediate diuresis may not be great the effect of oral mercupurin may be more prolonged than that produced by the parenterally administered drug. Thus, patients who reaccumulate edema rapidly and require intravenous medication at frequent intervals may accumulate their edema at a much slower rate, or not at all, when given the oral medication. Constant diuresis appears to be maintained in those patients who have experienced relief of their congestive heart failure.

Gold⁴ states that organic mercurials are usually eliminated completely, or almost so, in less than twenty-four hours and that a dose may be repeated every day with safety.

Regardless of the dosage and method of administration of the mercupurin tablets, toxic manifestations may occur. Such reactions do not usually limit the usefulness of the drug since they may not recur upon repeated or continued use of the tablets. Batterman et al.,^{2,3} in their study of hospitalized and ambulatory patients on their multiple dose schedules, found that the latter group of patients was more prone to develop gastrointestinal irritation, the explanation for which was not found.

In the patients on a daily dosage of the tablets Batterman et al.,³ found that the most common untoward reaction was digitalis toxicity in one-third of their ambulatory patients, which they believed was related to the phenomenon of mobilization of the digitalis from the edema fluid after diuresis was well established, i.e., after four to fourteen days of daily dosage when the existing edema was in the process of being removed. The signs of digitalis toxicity consisted in the development of auricular fibrillation, marked slowing of the ventricular rate in patients with auricular fibrillation and prolongation of A-V conduction time. Our patients showed none of these signs. Batterman et al.³ believed that the symptoms of gastrointestinal irritation (anorexia, nausea, vomiting or diarrhea) that developed during the administration of mercupurin tablets were due to digitalis toxicity rather than to mercurial irritation, because these symptoms subsided completely when digitalis was discontinued or decreased, even though the oral mercupurin was administered uninterruptedly. They stated that "we have no doubt that true gastro-intestinal irritation caused by the daily dose of oral Mercupurin may be en-

countered, although it was not observed in our series of patients." Although we cannot definitely exclude digitalis intoxication in some of our patients with toxic manifestations, we found no clear evidence that such was the case. While the gastrointestinal symptoms of digitalis toxicity and mercurialism may be similar, we considered the cramps, diarrhea and bloody stools in our patients to be due to mercurialism.

Gingivitis was uncommon and when it appeared it subsided after oral mercupurin therapy was discontinued. Batterman et al.³ observed that when the oral therapy was given a second time, two of their patients did not develop recurrence of the gingivitis. Our Case VII developed gingivitis on two occasions with subsidence each time after the drug was discontinued. After resumption of the oral mercupurin the gingivitis did not recur.

Increasing albuminuria with gastrointestinal symptoms in Batterman's patients occurred only in those with renal disease. Batterman et al.³ allowed a rest period of one week to patients receiving daily dosage of mercupurin tablets after the maximum effect of diuresis had been achieved and this was repeated every month. In our patients rest periods were not instituted.

CASE REPORTS

CASE I. F. A., a seventy-one year old woman with hypertensive and coronary heart disease was hospitalized from February 7, 1944 to March 7, 1944, and from April 25, 1944 to May 7, 1944, for treatment of congestive heart failure. After discharge on May 7, 1944, she required intravenous or intramuscular injections of mercupurin at weekly intervals. When the interval between injections was two weeks, symptoms recurred in the second week. On November 30, 1944, she was started on one mercupurin tablet twice a day for five days a week. She did well until March 7, 1945, when she exhausted her supply of mercupurin tablets

and promptly developed symptoms and signs of congestive heart failure. On March 22, 1945, she was given an intravenous injection of 2 cc. mercupurin and the mercupurin tablets were resumed; she again did well. In October and November, 1945, she experienced soreness of the abdomen without bowel symptoms when she took the mercupurin tablets. On January 1, 1946, she developed a grippal infection with recurrence of the congestive heart failure, in spite of the continued ingestion of the mercupurin tablets. On February 14, 1946 and February 21, 1946, she was given additional mercury in the form of intramuscular injections of 2 cc. mercupurin. On April 15, 1946, she suffered with an episode of rapid heart action of ten minutes' duration which was followed by the return of symptoms and signs of congestive heart failure. An intramuscular injection of 2 cc. mercupurin was given on April 25, 1946. The dosage of mercupurin was increased to one tablet three times a day for five days a week. Since then she has been free of congestive heart failure. Urine examinations have been repeatedly negative.

This case illustrates control of the signs and symptoms of congestive heart failure by orally administered mercupurin tablets. Exhaustion of the supply of the medication, a grippal infection and an episode of paroxysmal rapid heart action in spite of the continued ingestion of the tablets precipitated congestive heart failure and necessitated the temporary administration of mercupurin parenterally until the patient recovered her former reserve.

CASE II. L. B., a fifty-nine-year old man was hospitalized from January 6, 1944 to January 24, 1944, because of increasing effort dyspnea, nocturnal dyspnea and swelling of the ankles of five months' duration following myocardial infarction. The signs and symptoms of severe congestive heart failure disappeared after digitalization, two thoracenteses, four intramuscular mercupurin injections and a low salt diet with 6 Gm. NH_4Cl daily. He was hospitalized again from March 21, 1944 to April 7, 1944, with

congestive heart failure. Again, there was a good response to treatment and following his discharge from the hospital, he did fairly well with frequent intramuscular injections of mercupurin. Severe congestive heart failure recurred and he was again hospitalized in November, 1945. Following his discharge from the hospital, in spite of frequent injections of mercupurin and thoracenteses, the hydrothorax reappeared. On December 14, 1945, he developed a respiratory infection and on December 18, 1945, when the respiratory infection was clearing, he developed severe dyspnea which made necessary his readmission to the hospital on December 21, 1945 in a moribund state. The congestive heart failure responded promptly to therapy. Following his discharge from the hospital on January 13, 1946, he received intramuscular injections of mercupurin at intervals of two to three weeks, with relief of symptoms during the first week after the injection but with subsequent progressive development of signs and symptoms of congestive heart failure prior to the next injection. Mercupurin tablets, two every morning before breakfast, were started on September 6, 1946. On September 12, 1946, he felt well but on three occasions had abdominal cramps. The mercupurin tablets were continued without further cramps and on September 19, 1946, he reported that during the previous two days he experienced dyspnea on walking. The dosage of mercupurin tablets was increased to three every morning before breakfast.

He was free of signs and symptoms of congestive heart failure and showed repeatedly negative urines. On January 23, 1947, urine examination revealed 4 plus albumin. Unfortunately, this finding was not reported promptly and the drug was continued an additional week, at the end of which time the patient developed the picture of severe mercurialism. He was admitted to another hospital on February 4, 1947 in a state of shock. He developed renal insufficiency, hypochloremia, hypoproteinemia, anasarca and hypercholesterolemia; repeated attempts to increase the colloid osmotic pressure of the blood were unsuccessful. Symptoms of congestive heart failure were absent. He expired on March 7, 1947. Postmortem examination was not permitted.

The patient suffered severe recurrent congestive heart failure following acute myocardial infarction requiring repeated hospitalization, thoracenteses and mercurial injections. Complete relief was obtained with mercupurin tablets. Severe mercurialism developed and death occurred after one month.

CASE III. S. B., a fifty-eight year old woman with mild hypertension, constrictive pericarditis and ascites was treated by intravenous injections of mercupurin at seven to ten day intervals beginning in May, 1942. On February 8, 1945, she was given one mercupurin tablet daily with negligible effect. Beginning February 15, 1945, she took two mercupurin tablets every other evening at bedtime, ammonium chloride, 4.0 Gm. during the day and digitalis. On April 12, 1945, because of ascites and slight leg and sacral edema the dose of mercupurin was increased for two weeks to three tablets every other evening at bedtime. During this period on the mornings following the ingestion of the tablets, she suffered with abdominal cramps and two to three daily bowel movements. The dose was reduced to two tablets every other evening with control of the ascites. At present, in spite of taking the mercupurin tablets at bedtime, she sleeps well and at 5:30 the following morning voids and continues to diurese all that day. Urine examinations have been repeatedly negative.

This was a patient with constrictive pericarditis, ascites and edema, requiring frequent intravenous injections of mercupurin, effectively controlled with mercupurin tablets.

CASE IV. W. C., a fifty-four year old man with congestive heart failure and a history of myocardial infarction and hypertension, was treated with rest in bed, low salt regimen, digitalization, ammonium chloride and intravenous injections of mercupurin. Beginning October 7, 1943, weekly intravenous injections of mercupurin were necessary because of continuance of congestive heart failure. The results were unsatisfactory and on November 30, 1944, one mercupurin tablet twice a day for five days a

week was begun and after a week the dosage was increased to one tablet three times a day five days a week. Signs and symptoms of congestive heart failure disappeared but for purposes of study the plan of administration was changed to five tablets before breakfast twice a week and beginning on January 20, 1945 to five tablets once a week. Through February 10, 1945, the volume of urine after five tablets was approximately 2 quarts, less than after the intravenous administration of the drug. On February 11, 1945, he contracted a severe respiratory infection with abrupt development of congestive heart failure, requiring admission to another hospital for one month where he received intravenous injections of mercupurin every other day. He then continued the weekly ingestion of five mercupurin tablets until April 5, 1945, when the program of one tablet three times a day for five days a week was reinstituted because the patient believed that the urine volume was greater with the latter method of administration. He did well until April 19, 1945, when his supply of tablets was exhausted and for one week he was without them. Signs and symptoms of congestive heart failure recurred and required two intravenous injections of mercupurin at weekly intervals while he resumed the ingestion of the tablets three times a day for five days a week. Since then he has been free of congestive heart failure on this regimen. He has shown no evidence of mercurialism. Urine examinations have been repeatedly negative.

This case illustrates persistent congestive heart failure after myocardial infarction, despite repeated intravenous injections of mercupurin. No congestive failure occurred while taking mercupurin tablets. After the supply of tablets was exhausted and with development of a respiratory infection, recurrence of congestive heart failure was relieved by resumption of the mercupurin tablets and by several doses of mercupurin administered intravenously; the continuance of tablets orally was effective.

CASE V. W. D., a sixty-four-year old man with severe congestive heart failure and diabetes mellitus, was hospitalized from January 18,

1946 to February 10, 1946, with improvement on a regimen of bed rest, digitalization and insulin. The symptoms and signs of congestive heart failure soon recurred and persisted in spite of weekly injections of mercupurin. On May 16, 1946, he was started on three mercupurin tablets every morning before breakfast with striking improvement. Since then he has been free of congestive heart failure. He has shown no evidence of mercurialism. Albumin has been present consistently in slight amounts and the sediments were negative.

This was a patient with persistent congestive heart failure despite repeated injections of mercupurin; he showed dramatic response to therapy with oral mercupurin tablets.

CASE VI. J. G., a fifty-six-year old man with luetic heart disease, congestive heart failure and angina pectoris, did not improve on the usual treatment for congestive heart failure. On December 14, 1944, he was given one mercupurin tablet three times a day in addition to his other treatment, with marked improvement of congestive failure. On January 5, 1945, he developed bloody stools and cramps and the mercupurin tablets were omitted for several days. At this time the dyspnea on effort was markedly improved. In February and March, 1945, he had bouts of diarrhea and cramps, each lasting one day but the mercupurin tablets were continued. Following an upper respiratory infection in March, 1945, the nocturnal anginal attacks with dyspnea increased. Beginning in April, 1945, he was free of dyspnea but continued to suffer with angina by day and at night. In August, 1945, on three occasions he had diarrhea lasting one day. On October 4, 1945, he died suddenly. Throughout the period of observation the urine showed slight amounts of albumin and the sediments were negative.

This case illustrates persistent congestive failure in spite of mercupurin injections in a patient with luetic heart disease. Mercupurin tablets relieved the congestive heart failure but the anginal attacks persisted and the patient died suddenly.

CASE VII. M. O., a seventy-four year old man with aortic stenosis and insufficiency, as well as angina pectoris, was hospitalized in June, 1943, for progressive congestive heart failure of six months' duration. With rest in bed, low salt diet, digitalization, ammonium chloride, four intravenous injections of 2 cc. mercupurin and bilateral thoracentesis he rapidly improved. In September, 1943, and January, 1944, he was readmitted because of recurrent congestive heart failure and on a similar therapeutic program, including six intravenous injections of 2 cc. mercupurin, he improved but continued to have frequent angina pectoris. In October, 1944, congestive heart failure recurred, for which he was given intramuscular injections of 2 cc. mercupurin on October 5, 1944, November 16, 1944 and November 30, 1944, with good diuretic responses. Following the last injection one mercupurin tablet twice a day was given with good effect. On December 7, 1944, the dose was increased to three tablets every morning. On December 14, 1944, he reported a brief period of abdominal cramps with one bowel movement a day. On December 21, 1944, he complained of pain and an itchy feeling in the gums with anorexia. No symptoms or signs of congestive heart failure were observed. The mercupurin tablets were omitted until January 11, 1945, when the gums were normal but the patient complained of dyspnea. An intramuscular injection of 2 cc. mercupurin was given at this time and one mercupurin tablet three times a day for five days a week was resumed. On this regimen he did well until May 1, 1945, when he again complained of pain in the gums and teeth. The lower gums were spongy and covered with exudate; there was no mercury line. The mercupurin tablets were omitted from May 17, 1945 to June 28, 1945, during which time the gums became normal except for pyorrhea. However, congestive failure recurred and two mercupurin tablets every other morning were resumed; the congestive failure cleared up. On August 30, 1945, the dosage of mercupurin tablets was reduced to one tablet every other morning to determine if the patient would remain symptom-free on the smaller dosage. Because he developed dyspnea on effort, on September 20, 1945 the dosage of mercupurin tablets was

increased to two every other morning. On October 4, 1945, after his supply of mercupurin tablets was exhausted for three days he again developed recurrence of dyspnea on effort and also paroxysms at night which woke him from sleep. Mercupurin tablets, one daily, were resumed and he did well until January 14, 1946, when exertional and paroxysmal nocturnal dyspnea recurred. Intramuscular injections of 2 cc. mercupurin were given on January 31, 1946, February 7, 1946 and February 14, 1946, with good diuretic responses and the patient became free from symptoms. On March 14, 1946, the dosage of mercupurin was increased to two tablets five times a week and the patient became free from symptoms of congestive heart failure. On July 5, 1946, the patient expired in his sleep. Minimal albuminuria was present throughout the period of observation.

This patient had recurrent congestive heart failure with aortic stenosis and insufficiency and angina pectoris. Mercupurin tablets relieved the congestive heart failure but did not alter the angina pectoris; the patient died suddenly.

CASE VIII. M. P., a sixty-five year old man with hypertension and angina pectoris since 1935, developed congestive heart failure in 1941. He was hospitalized from May 13, 1942 to June 2, 1942, for the treatment of congestive heart failure. With rest in bed, a salt-poor diet, digitalization and thesodate tablets he rapidly improved. Mercurials were not necessary. Five months following his discharge the symptoms and signs of congestive heart failure recurred in spite of continuance of treatment and beginning in January, 1943, intravenous mercurials were given at weekly or bi-weekly intervals. In November, 1944, in spite of this treatment and occasional urea administration, the signs and symptoms of congestive heart failure required two intravenous injections of mercurials a week. At the same time he was given one mercupurin tablet twice a day. After one week severe orthopnea recurred and the dosage of mercupurin tablets was increased to three every morning before breakfast. After one week the mercupurin tablets were discontinued because they pro-

duced no demonstrable effect. The mercurial injections were continued semiweekly until February, 1945, when he took five mercupurin tablets twice weekly for two weeks without any effect. The mercurial injections were then given weekly or semiweekly throughout the remainder of 1945 and up to October 10, 1946. For one week in May, 1946, he was given three mercupurin tablets each morning without any demonstrable effect. Beginning on August 1, 1946, after he had been receiving semiweekly injections of mercurials for a month, he was given two mercupurin tablets every morning before breakfast. Beginning August 8, 1946, the dose was increased to three tablets every morning. Improvement of the congestive heart failure resulted but he still required weekly injections of mercurials. Because of recurrence of severe congestive heart failure he was hospitalized in October, 1946, with marked improvement. Since his discharge he has taken digitalis, ammonium chloride and three mercupurin tablets each morning and has been free from congestive heart failure. Urine examinations revealed moderate albuminuria and negative sediments throughout his illness.

This was a patient with chronic congestive heart failure who required weekly or semiweekly injections of mercurials. Because the results were not satisfactory, oral mercupurin was given but with poor results because of gross congestive heart failure. After adequate treatment of congestive failure in the hospital, oral mercupurin was effective.

CASE IX. G. P., an extremely obese forty-four year old man, had an attack of posterior myocardial infarction in 1934. In 1941 and 1943, he was admitted to another hospital because of congestive heart failure, obesity, alcohol addiction and hypertension. Treatment consisted of digitalization, rest in bed and intravenous injections of mercurials. He was admitted to the Beth Israel Hospital in February, 1944, because of increasing congestive heart failure of two to three weeks' duration as well as angina pectoris. With rest in bed, digitalization, four intravenous

injections of mercupurin, ammonium chloride and an 800 calory low-salt diet, the patient improved dramatically. He was again hospitalized in August, 1944, for treatment of severe congestive heart failure, with marked improvement. After his discharge from the hospital he was treated with digitalis, ammonium chloride, a low-salt diet, vitamin B complex and thiamin chloride. Two cc. of mercupurin were given intramuscularly and repeated on November 2 and November 9, 1944, for signs of congestion. On March 30, 1945, he was again in severe congestive heart failure, having omitted all medication, and he was again hospitalized, with improvement. Congestive failure recurred and hospitalization was again necessary in October, 1945. He was started on three mercupurin tablets every other morning before breakfast, in addition to the other treatment. On this regimen he was free from signs and symptoms of congestive heart failure until May 2, 1946, when he reported that his supply of mercupurin tablets had been exhausted one week previously. At this time he felt very well and showed slight edema of the legs. He was given 2 cc. mercupurin intramuscularly and was instructed to resume the former plan of therapy. On May 16, 1946, he felt well but because of the presence of a slight amount of fluid at both lung bases and slight edema of the legs, he was given 2 cc. mercupurin intramuscularly. The dosage of mercupurin tablets was increased to three every morning before breakfast. On May 23, 1946, he still showed evidence of fluid in both lungs and slight edema of the legs. Two cc. of mercupurin were administered intramuscularly. On June 26, 1946, he felt well but he showed slight edema of the legs and 2 cc. of mercupurin were administered intramuscularly. On August 15, 1946, he presented less edema of the legs and received 2 cc. mercupurin intramuscularly. On September 19, 1946, he was free from signs and symptoms of congestive heart failure. On December 16, 1946, he suffered with an attack of nocturnal paroxysmal dyspnea after a very heated argument. Since then he has been free of congestive heart failure. Repeated urine examinations during the period of oral mercupurin therapy revealed no albumin.

This was a patient with recurrent severe congestive heart failure and coronary and hypertensive heart disease who required frequent hospitalization. The patient obtained complete freedom from signs and symptoms of failure on oral mercupurin therapy. After the supply of tablets was exhausted there was a recurrence of signs of congestive heart failure which were relieved by resumption of the mercupurin tablets and several doses of mercupurin administered intramuscularly; the continuance of tablets was effective.

CASE X. J. S., a seventy-one year old man with hypertensive heart disease, developed congestive heart failure in April, 1944. He was digitalized but was not very cooperative. In April, 1945, he had severe congestive heart failure. He was redigitalized and ammonium chloride and a low salt regimen were prescribed. An intravenous injection of 2 cc. mercupurin was given on April 26, 1945 and May 3, 1945, with profuse diuresis with recurrence of symptoms and signs of congestive heart failure between injections. On May 10, 1945, he received an intravenous injection of 2 cc. mercupurin and mercupurin tablets were started with a dosage of one tablet three times a day for five days a week. Congestive heart failure recurred and on May 17, 1945, an intravenous injection of 2 cc. mercupurin was given and three mercupurin tablets every other morning were prescribed. Because the congestive heart failure could not be controlled with weekly intravenous injections of mercupurin, mercupurin tablets, digitalis and ammonium chloride the patient was admitted to the hospital on June 25, 1945. With rest in bed, digitalis, low-salt regimen, ammonium chloride and three intramuscular injections of mercupurin he rapidly improved and was discharged on July 11, 1945. On July 19, 1945 and July 26, 1945, he received an intravenous injection of 2 cc. mercupurin and he took three mercupurin tablets three days after each injection. On August 2, 1945, he received an intravenous injection of 2 cc. mercupurin and the mercupurin tablets were resumed, three every other morning before

breakfast. In October, 1945, after a prolonged attack of nocturnal paroxysmal dyspnea, the digitalis was increased to 0.2 Gm. daily. Thereafter, he was free of signs and symptoms of congestive heart failure until April, 1946, when after omitting the mercupurin tablets for one week he developed sudden onset of dyspnea and was admitted to another hospital. Examination there revealed evidence of mild congestive heart failure. After his discharge he was observed there until October 10, 1946, when he returned to us for a follow-up visit. He reported that in the six months' interval he received intramuscular injections of mercupurin, digitalis 0.1 Gm. daily, ammonium chloride but no mercupurin tablets; he had dyspnea on effort and no edema.

This was a patient with hypertensive heart disease and congestive heart failure who improved rapidly on a regimen of weekly intravenous injections. Mercupurin tablets were started during gross congestive failure but were ineffective. He was hospitalized with resultant clearing of the congestive failure; he was then maintained on mercupurin tablets and was in a greatly improved condition. Recurrence of congestive failure occurred when the tablets were discontinued.

CASE XI. I. W., a sixty-eight year old woman with congestive failure, nodular thyroid, blood pressure of 224/125, great enlargement of the heart and basal metabolic rate of +10 per cent, had a total bilateral thyroidectomy on November 6, 1944. Two weeks after her discharge she developed exertional dyspnea and orthopnea as well as edema of the legs. She was readmitted to the hospital on December 26, 1944, for treatment of congestive heart failure, with improvement. Intravenous injections of 2 cc. mercupurin were continued after discharge and in April and May, 1945, there was no evidence of congestive failure. On January 3, 1946, moderately severe congestive heart failure was again evident. On January 24, January 31, 1946 and February 7, 1946, intramuscular injections of 2 cc. mercupurin were given but the congestive heart failure became more severe and she was hos-

pitalized from February 11, 1946 to March 5, 1946. On March 21, 1946, she developed moderately severe congestive heart failure after a respiratory infection. An intramuscular injection of 2 cc. mercupurin was given and mercupurin tablets, three every other morning before breakfast, were prescribed. Because of slight edema of her legs a parenteral dose of mercupurin was given on April 25, 1946. She improved remarkably and has continued to be free from signs and symptoms of congestive heart failure. From August, 1946 to December, 1946, she was aware of a lack of appetite and slight nausea without cramps or diarrhea on the days she took the mercupurin tablets. Since December, 1946, she has taken the three mercupurin tablets every other evening at bedtime and has been free of nausea and anorexia, as well as of congestive heart failure. The urine examinations have shown slight to moderate amounts of albumin with negative sediments.

The patient had recurrent severe congestive heart failure with marked hypertension and great cardiac enlargement which required frequent hospitalization. She has had complete freedom from symptoms and signs of failure since institution of oral mercupurin therapy; parenteral mercurials were not necessary during this period.

SUMMARY

1. The oral administration of mercupurin tablets is valuable in the treatment of

ambulatory patients with chronic congestive heart failure.

2. Oral administration of mercurial diuretics may be more practical and more effective than parenteral administration in some ambulatory patients with chronic or recurrent congestive heart failure.

3. The method of administration and dosage must be individualized to obtain satisfactory results.

4. Minor toxic manifestations occur in some patients but offer no serious obstacle to the continuance of treatment, provided that the patients are carefully followed.

5. One instance of severe mercurialism was observed which makes it necessary to stress the importance of adequate supervision of patients receiving this drug. Unless patients can be seen once a week for the necessary clinical and laboratory examinations, oral mercupurin therapy should not be used.

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Pathogenesis of Peripheral Cardiac Edema*

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OVER a period of many years the pathogenesis of cardiac edema has interested physiologists and clinicians. The more recent studies of peripheral edema have not only elaborated upon and expanded older conceptions but these investigations also have suggested other possible mechanisms of edema formation. The subject is of sufficient current interest and the significant contributions are so widely scattered in the literature that a general survey of the question now seems warranted.

A century ago, James Hope³⁴ attempted to explain the symptoms and signs of cardiac decompensation on the basis of pulmonary and systemic venous stasis from failure of the weakened heart. Studies with the heart-lung preparation suggested to Starling⁷³ that cardiac failure leads directly to an increase in venous pressure. In the ensuing years, the importance of venous engorgement was emphasized by a number of observers, including many French and German clinicians (Harrison³⁰).

In recent years, the hypothesis that venous engorgement is primarily concerned in cardiac edema has been championed by Harrison³⁰ under the designation of "backward failure." Harrison maintained that elevated venous pressure is the result of the impounding blood in the systemic veins as the ability of the heart to pump blood forward becomes impaired. The rise in venous tension then leads to increased capillary pressure, augmented filtration and thence edema. Increased capillary permeability, partial lymphatic obstruction and decrease in plasma proteins have been suggested as

secondary factors in such tissue fluid retention.^{19,30}

Although it has been widely held that congestive phenomena dominate the mechanisms producing the edema of heart failure, there is a growing body of evidence to indicate that certain signs of cardiac failure arise in consequence of altered cardiac output. Nearly one hundred years ago, Stokes⁷⁷ emphasized the importance of myocardial weakness as the precipitating factor in heart failure. Mackenzie,⁵⁰ in later years, suggested that the primary cause of the symptoms of cardiac insufficiency is a deficient blood supply to the tissues. In the light of newer researches into the mechanisms of cardiac failure, these older suggestions have assumed new significance. In contrast to the older hypothesis of "backward failure," the conception of "forward failure" of the heart, as it may be conveniently designated, has been regarded with increasing interest in recent years.

The forward failure hypothesis has been elaborated upon by the work of Warren, Stead and associates.⁸¹ These investigators called attention to the well known fact that subclinical or occult edema is present earlier in heart disease than is frank edema. They suggested that elevation of venous tension may occur later than extracellular fluid retention; therefore, increased venous pressure may be of secondary importance in the pathogenesis of edema. In addition, they suggested that renal function may be disturbed during cardiac failure so that sodium chloride is retained by the kidneys. Reten-

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tion of fluid by the body tissues then ensues. (Fig. 1.)

The clinical and experimental evidence of the various suggested mechanisms of edema formation will be briefly reviewed.

Such efforts have been fraught with difficulty and have not yielded uniform results. In 1929, Grollman²⁸ evolved the acetylene technic which was subsequently utilized by a number of workers as the most accurate

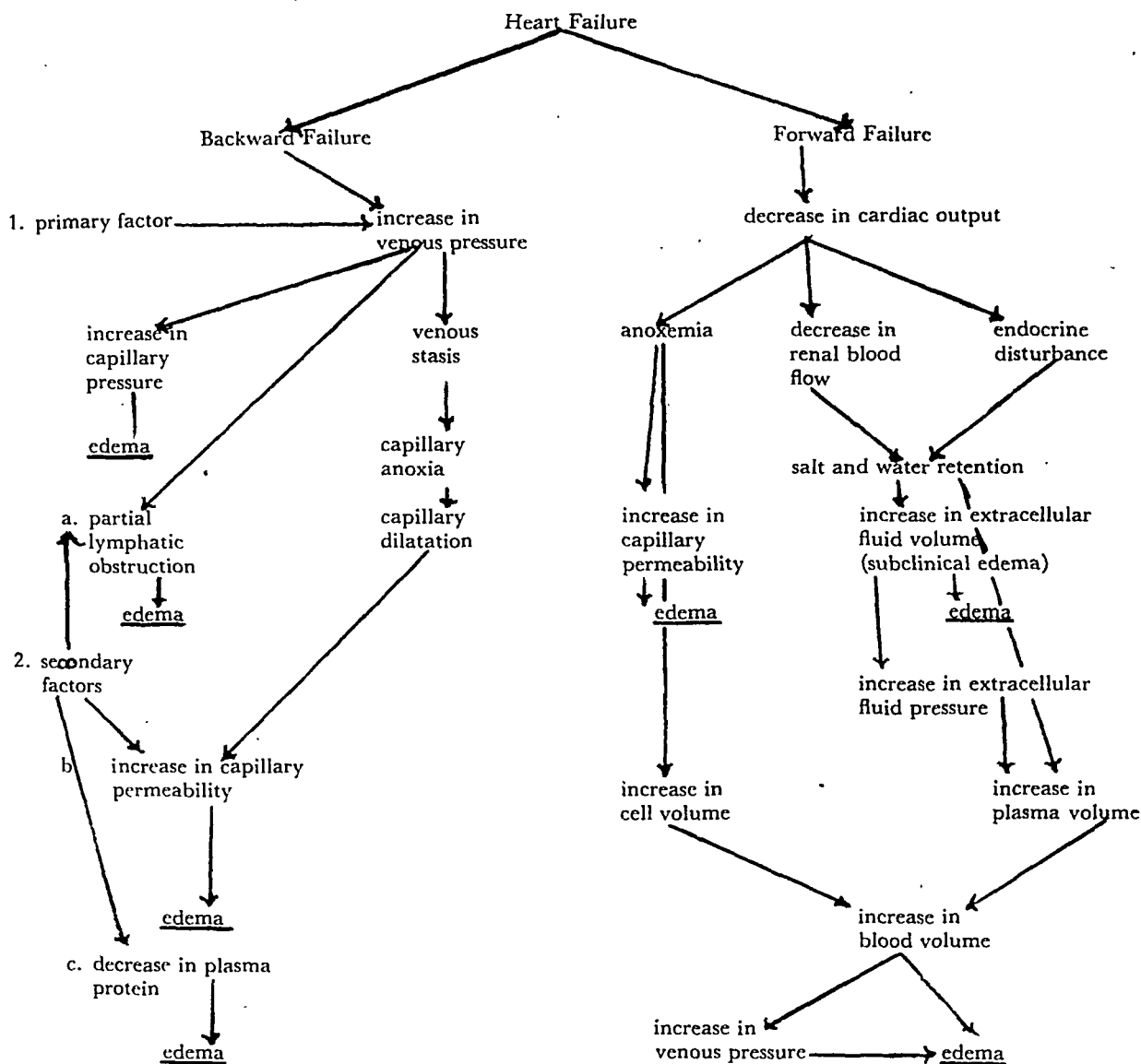


FIG. 1.

Cardiac Output. The output of blood by the heart during cardiac decompensation is suggested as of primary importance in a consideration of the mechanism of edema formation. The very basis for a theory of "forward failure" must obviously depend upon the demonstration of diminished cardiac output. Investigators have endeavored for years to evolve an accurate method for the determination of cardiac output in man.

procedure. Harrison,³⁰ in a summary of the evidence obtained by this method, enumerated four important considerations: (1) apparently normal subjects may have a low cardiac output; (2) the cardiac output may be elevated, diminished or normal in patients with congestive heart failure; (3) average values and ranges of cardiac output are similar in cardiac patients with and without heart failure and (4) with clinical

improvement and disappearance of edema there may be an increase, decrease or no change in the output of the heart. These findings suggest that the cardiac output is not consistently decreased during heart failure. However, some doubt has been cast upon the validity of this evidence by the criticism which has been leveled at the acetylene method. Hoff³² has pointed out that a major source of error may occur in the technic, in the matter of recirculation of blood. The same criticism applies to any method involving the calculation of circulating substances in the blood stream.

Many years ago, Fick¹⁸ evolved a unique method of determining cardiac output. The method depended upon calculation of the volume of blood passing through the pulmonary vascular bed as determined by measuring (1) the uptake of oxygen by the venous blood passing through the lungs and (2) the rate of oxygen consumption. Similar calculations may be made from equivalent data concerning carbon dioxide. The method has been extensively used and the details of the calculations need not be repeated here. As originally utilized by Fick,¹⁸ the procedure entailed the gas analyses of peripheral venous and arterial blood. However, the utilization of a sample of peripheral venous blood from one extremity obviously may not represent the oxygen or carbon dioxide content of venous blood entering the right ventricle and pulmonary artery.¹⁹

More recently the Fick principle has become of inestimable value with the development of the technic of right heart catheterization.²⁰ With this procedure, it is possible to sample venous blood from the right auricle or ventricle. Arterial blood is obtained from a convenient point in the periphery. The cardiac output can be determined with greater accuracy than by use of the acetylene technic. Klein³⁸ was one of the first workers to measure cardiac output in man by this method but it was not used extensively until recently because of the danger to the patient which was thought to accompany the procedure. Cournand and his associates,⁹ using the same method, re-

ported studies of cardiac output in thirteen normal subjects. They obtained average values for the cardiac index* of 3.12 L. per sq. m. per min. These values were 26.8 per cent higher than those previously reported using the acetylene method.

The technic of right heart catheterization was employed by Merrill⁵⁴ to measure cardiac output in patients with congestive heart failure. He found a normal range of cardiac index of 2.3 to 4.1 (L. per sq. m. per min.) with an average value of 3.3. The cardiac index in twenty-three cases of heart failure was below the average normal value of 3.3 in twenty of the cases. In ten of these twenty cases the cardiac index was below 2.3 which is the lower limit of normal. These data demonstrate a definite trend toward a low cardiac output in congestive heart failure.

Two criticisms have been advanced by Harrison against the contention that the cardiac output is decreased during heart failure. First, he pointed out that measurements of cardiac output have failed to demonstrate low values in all patients with cardiac decompensation. Furthermore, cases were cited in which clinical improvement was not accompanied by a significant change in cardiac output. These observations by Harrison are not necessarily irreconcilable with the forward failure hypothesis. Several workers^{19, 29, 54} have pointed out that many factors influence cardiac output; all cases would not be expected to show a decrease at any given moment during cardiac decompensation. For instance, anxiety has been shown to increase the cardiac output remarkably.⁷⁶ When cardiac compensation was accomplished with mercurial diuretics in the cases cited by Harrison, the output might not be expected to change.⁵¹ Merrill⁵⁴ used digitalis to abolish heart failure. All of six patients then showed an increase in cardiac output.

Second, Harrison called attention to patients with peripheral circulatory collapse in whom the cardiac output was markedly de-

* Cardiac index is the minute volume output of the heart per square meter of body surface.

creased and the clinical picture was not that of heart failure, with dyspnea and edema. Merrill⁵⁴ answered the second objection in indicating that the duration of shock is usually too short to permit the accumulation of salt and water to occur. Edema develops if shock is prolonged.^{54, 55}

Renal Blood Flow. It has been known since the time of Richard Bright that certain forms of renal disease are accompanied by peripheral edema. For many years clinicians believed that edema from kidney disease and heart failure was produced by quite different mechanisms. However, the experimental and clinical evidence of recent years has suggested that the part played by the kidney in the pathogenesis of cardiac edema may be of some significance. The possibility of such a "renal factor" is indicated in the observations of Fremont-Smith.^{21, 22} He noted that ingestion of large amounts of water by patients with cardiac edema resulted in greater dilution of the blood and less diuresis than occurs in normal persons.

An interesting conception of the rôle of the kidneys in the pathogenesis of cardiac edema was offered by Warren and Stead⁸¹ in 1944. They suggested that under the impact of decreased cardiac output, diminished renal flow impairs the excretion of salt by the kidneys and that such sodium chloride retention provokes abnormal water storage and the formation of edema. The evidence supporting this conception will be presented in some detail.

In recent years, improved methods of measuring renal blood flow have been developed. A preliminary report by Warren and Stead⁸² demonstrated that a reduction in blood flow through the kidney occurs in the course of heart failure. To determine renal blood flow, (1) they used the para-amino hippurate clearance technic, and (2) they catheterized the renal vein in man in order to obtain renal venous blood for measurement of its oxygen content. An increase in the arteriovenous oxygen difference in the kidney during congestive heart failure was interpreted as indicating that the quantity of blood passing through the kidney was

reduced. Merrill⁵⁴ also employed the para-amino hippurate clearance method to study renal blood flow in a series of patients with cardiac decompensation; he found a marked reduction in renal flow in each case. Glomerular filtration rate decreased less than the renal blood flow; this resulted in a high filtration fraction which suggested to Merrill that efferent arteriolar constriction had occurred. Since renin is known to cause efferent arteriolar constriction,⁵⁶ Merrill⁵⁵ bio-assayed the blood for renin in patients with heart failure. He found a significant amount of renin in renal venous blood in eight of eleven patients.

Merrill's study indicated that the reduction in renal blood flow was usually proportionately greater than the decrease in cardiac output. He ascribed this reduction to the diversion of blood from the kidney. The increase in renal blood flow accompanying clinical improvement in some of these patients was not marked because compensation was accomplished by means of mercurial diuretics alone and the cardiac output remained low. Phenol red clearance studies by Seymour and his co-workers⁶⁹ showed an increase in renal blood flow of approximately the same degree as the cardiac output when compensation was accomplished with digitalis.

Unfortunately, it is difficult to prove a direct correlation between reduced renal blood flow and the pathogenesis of cardiac edema for it may be argued that the changes in the renal circulation are secondary to an increase in venous pressure. Nevertheless, Merrill's results support the pathogenic rôle played by diminished renal flow in that: (1) no significant correlation between the level of venous pressure and renal flow occurred and (2) the renal blood flow remained below 50 per cent of normal in most cases, despite a marked reduction in venous pressure.

The question now arises as to whether reduced renal blood flow will lead to salt retention. Reaser and Burch,⁶¹ using radioactive sodium, demonstrated a marked impairment in sodium excretion in patients with cardiac decompensation. Fletcher and

Schroeder²³ found that patients in congestive heart failure excrete only 30 per cent as much salt as normal subjects when large amounts of salt are given by venoclysis. These observations suggested a disturbance in salt metabolism during cardiac insufficiency. Fitcher and Schroeder tentatively suggested that a circulatory disturbance in the kidney may lead to renal anoxemia and that an increase in the rate of tubular reabsorption of sodium chloride occurs. However, actual determinations of tubular reabsorption show that it is normal or slightly decreased during heart failure.⁵⁴ The studies of Seymour and his co-workers⁶⁹ also showed that tubular function does not appear to be greatly impaired during heart failure. They found no change in the concentrating power of the kidney during cardiac compensation.

Possibly a more satisfactory explanation of salt retention is a low glomerular filtration rate secondary to definite reduction in renal blood flow. Merrill⁵⁴ demonstrated that glomerular filtration (inulin clearance) may be reduced 33 to 50 per cent of normal in patients with cardiac insufficiency. This study may indicate that the quantity of sodium filtered by the glomerulus is decreased. Then if tubular resorption is essentially normal during heart failure and reduced sodium filtration occurs, sodium ions must be retained in the body. The sodium retention affects body water retention and a corresponding increase in blood and tissue fluid volume results. Therefore, it is easily understood that with the patient in heart failure who continues to use an average salt-containing diet, retention of sodium chloride and water may be enhanced and clinical edema of varying degree may ensue. In addition, it has been pointed out⁵⁴ that glomerular filtration rate may be very low in chronic nephritis and, in such cases, edema may be marked although not invariably so.

Venous Pressure. According to the hypothesis of "backward failure," venous engorgement results from the impounding of blood in the systemic veins. The events

which may lead to an elevated venous pressure are summarized in considering the development of congestive heart failure in a patient with hypertension (Harrison³⁰). Let us assume that the left ventricle normally expels 40 cc. of blood per beat. As a result of hypertension, the myocardium weakens and the left ventricle expels only 39 cc. Inflow continues to be 40 cc. so that the left ventricle receives more blood than is expelled. Dilatation of the left ventricle then occurs and the ventricular pressure rises. A difference in the pressure between the left ventricle and auricle occurs so that the blood received by the left ventricle is reduced to 39 cc. per beat. Since the left auricle is highly distensible, it dilates to retain blood before the pressure eventually rises. Fibers of the left ventricle, under the stretch of dilatation, contract more strongly and are again able to deliver 40 cc. of blood per beat. Equilibrium is temporarily restored with the same cardiac output, a larger diastolic heart size and a higher pulmonary venous pressure. Extension of this process to include the right ventricle and the right auricle results finally in an increase in the pressure in the systemic veins.

Harrison contended that this explanation of the symptoms of heart failure is the most satisfactory.³⁰ To illustrate, he reasoned that congestive phenomena should occur first in the lungs and later in the systemic circulation. In support of this hypothesis is the added finding that a decrease in vital capacity may precede an elevation of venous pressure.³⁰

Recent studies by Landis and his associates⁴⁵ have emphasized again the mechanical elements concerned in the elevation of venous pressure in heart failure. In their clever experiments, they "exercised" normal anesthetized dogs by applying appropriate electrical stimuli to the extremities, producing muscular motion. During such muscular activity a fall in venous pressure occurred. However, when the hearts of dogs were previously damaged by interference with the coronary circulation, such muscular activity produced a rise of venous pres-

sure. This evidence suggested to them that chronic congestive heart failure might result from repeated episodes of increased muscular activity in individuals with impaired cardiac "competence." During these periods blood accumulates in the systemic veins due to back pressure, leading to increased transudation into the tissues. Thereafter, a reduction in "effective blood volume" occurs due to impounding of blood in the venous system with compensatory systemic vasoconstriction and retention of salt by the kidneys. Landis et al., reasoned that "the division between 'backward failure' and 'forward failure' becomes somewhat less rigid because the former may, through changes in effective blood volume, lead during activity to the latter."

Many workers^{1,54,55,70,74,75,81} have considered backward failure and venous engorgement an unduly simple explanation and have suggested that additional factors are probably concerned. Ryder⁶⁵ reported that an elevated tissue pressure may exert considerable influence on venous tension. Evidence indicates that tissue pressure is elevated in cardiac failure and some observers^{74,75} have suggested that venous hypertension may be partially referable to such elevated tissue tension. It has also been demonstrated that an increase in intrapleural pressure (occurring as in hyperpnea or Valsalva effect) contributes to the elevation of venous tension.^{9,23,84} These factors do not appear to be essential to the increase of venous pressure accompanying cardiac failure but they may be of some significance.

Of some interest is the possibility that changes in venous pressure occur because of redistribution of blood within the vascular bed from alterations in the tone of the vascular system.^{4,55} Certain clinical observations, such as the maintenance of a normal blood pressure in the presence of decreased cardiac output and the early fall in venous pressure which occurs in response to digitalis, indicate that vasoconstriction occurs.⁵⁵ Additional evidence for active vasoconstriction is the increased peripheral resistance frequently noted during cardiac decompensation.⁶⁹

The pathogenesis of vasoconstriction in congestive heart failure is not satisfactorily understood. Forward failure theorists have suggested that vasoconstriction may be secondary to decreased cardiac output.⁵⁵ On the other hand, Landis maintained that the

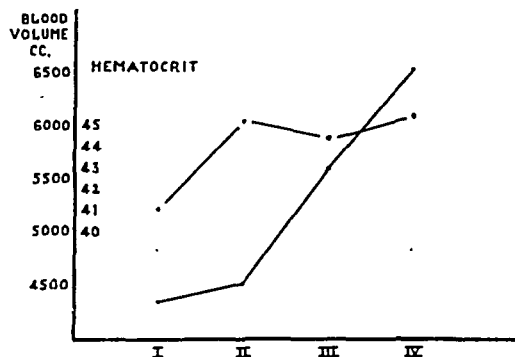


FIG. 2. Changes occurring in blood volume and hematocrit as the degree of cardiac decompensation increases (Gibson and Evans, 1937).²⁴ Group I consisted of patients with valvular heart disease who exhibited no symptoms or signs of cardiac insufficiency. Group II included those with mild symptoms of cardiac decompensation. In groups III and IV the patients were in severe congestive heart failure. — and - - - are symbols for blood volume and hematocrit, respectively.

vasoconstriction is compensatory in reaction to venous engorgement. Renin, which has been found in renal venous blood of patients with heart failure,⁵⁵ may be related to the vasoconstriction but this relation is not clear.

Another factor which has been considered of importance in explaining the mechanism of venous hypertension is increased blood volume. That hypervolemia occurs during congestive heart failure is well established. Gibson and Evans,²⁴ using a dye method, studied seventy-three patients with clinically proved heart disease. (Fig. 2.) A marked elevation of blood volume occurred as the degree of heart failure increased although the hematocrit remained almost unchanged. These findings indicated that cell volume increased in nearly the same order of magnitude as the plasma volume. The experiments were confirmed by the observations of Walker et al.⁸⁰ and by Meneely and Kaltreider.⁵³ The latter authors noted a high correlation between the degree of anoxemia and the increase in cell volume.

Observations by Landis and his co-workers⁴⁵ do not support the hypothesis that hypervolemia is the principal factor leading to venous hypertension. They increased the blood volume in normal dogs from 50 to 100 per cent by transfusion and found only a transient elevation in venous tension. In these transfused dogs, a sustained rise in venous pressure did not occur during exercise. On the other hand, Starr and his associates^{74,75} found that the venous pressure of patients with heart failure remained elevated after death; therefore, they reasoned that postmortem persistence of venous hypertension must be due to increased volume of fluid in the vascular bed.

The time relationship of the appearance of an elevation of venous pressure to the rise in plasma volume and the onset of edema is of considerable importance. If the plasma volume increases and subclinical or frank edema occurs *before* the venous pressure becomes elevated, then hypervolemia may be the principal cause of elevated venous pressure. In order to investigate this question, Warren and Stead⁸¹ studied two cardiac patients as they developed "heart failure" following salt administration. The data of one case are presented:

The case was that of a fifty year old negro man with hypertensive and arteriosclerotic heart disease in severe heart failure. With treatment, including digitalis, bed rest, diuretics and a salt-free diet cardiac compensation was restored. Thereafter, salt was added to his diet; diuretics were omitted but he continued to receive digitalis. During the following nine days an increase in plasma volume and in body weight occurred but the venous pressure remained essentially unchanged.

In these two cases, the curves of weight and plasma volume were essentially parallel, indicating that elevation of venous pressure does not necessarily accompany hypervolemia and the formation of edema.

Several investigators have demonstrated that errors occur in the use of the T-1824 dye technic for plasma volume determination.^{17,25,27} This method was used in the

above described observations. The loss of dye into the extracellular spaces or lymphatic system during mixing and the infiltration of dye into the renal and hepatic parenchyma are objections to this method.^{17,25,27,46} Hopper and his co-workers^{35,26} concluded that this method was valuable only for demonstrating gross changes in blood volume and not for determining absolute values. Since Warren and Stead studied only two cases and since the dye method is not considered completely reliable, one is rather hesitant to accept their evidence of the temporal relation of venous pressure and plasma volume changes as conclusive. Their observations, however, are suggestive.

Another question arises concerning the evaluation of the evidence of Warren and Stead. Certain factors of heart failure (e.g., rise in venous pressure and a gain in weight) appeared in patients with compensated heart disease following salt administration. Lyons et al.⁴⁹ and Grant and Reichsman²⁶ showed that administering salt to normal subjects will result in an increase in venous pressure, plasma volume and weight. If indeed this occurs in normal individuals, one wonders whether the changes that occurred in the two cases of Warren and Stead represent true congestive heart failure. The problem cannot be answered definitely but it is true that the clinical picture in these cases closely simulated heart failure.

That salt and water retention occurs in heart failure is supported by the observation that an increase in weight and the appearance of edema may occur prior to the elevation of venous pressure. An increase in weight preceded the rise of venous pressure in the two cases of Warren and Stead⁸¹ and Altschule¹ found that seven of fifteen patients with edema had venous pressures of 75 mm. of saline or less. There are other reports in which elevation of venous pressure and edema were not associated^{2,3,37,63} or did not correspond in magnitude. In some cases, the disappearance of edema was followed, and not preceded, by a lowering of venous pressure. Such findings point to the possi-

bility that an increase in venous pressure may not be the primary factor in the formation of edema.

Clinical observations offer additional evidence that retention of extracellular fluid precedes a rise in venous pressure. Patients with paroxysmal nocturnal dyspnea, without venous engorgement and clinical edema, may show striking improvement when the urinary output is increased by the use of mercurial diuretics.¹⁹ In left-sided heart failure, dyspnea and orthopnea may develop before the venous pressure becomes elevated yet there is often subclinical edema as shown by weight gain. A decrease in weight of several kilograms may occur with restoration of cardiac compensation.⁸¹

In contrast, Reichsman and Grant⁶² studied the temporal relation of the appearance of elevated venous pressure, increase in weight and edema in three patients with "inactive" rheumatic heart disease. These patients were in congestive heart failure upon entrance to the hospital; cardiac compensation was accomplished with digitalis and a low salt diet. Digitalis medication was then discontinued. They found that a rise in venous pressure preceded the gain in weight and the appearance of edema in each of these patients. The omission of digitalis from the therapeutic regimen allowed the myocardium to fail again. Consequently, this experiment more closely simulates naturally occurring heart failure than the one performed by Warren and Stead. The observations of Reichsman and Grant support the back pressure hypothesis. Another interpretation of these findings is that the rise in venous pressure may be the result of redistribution of blood in the venous system produced by venoconstriction.⁵⁴

The question of the temporal relation of venous hypertension to edema formation has not been conclusively answered. Further experiments with particular reference to venous pressure determinations are desirable. It would be preferable to measure right auricular pressure instead of venous pressure but the technical difficulty of this procedure makes it impractical for repeated

use in the same patient. To establish conclusively the time relation of elevated venous pressure and edema, a large series of cases must be studied.

Whatever the origin of venous engorgement, it seems that an elevation of venous pressure to a certain critical level will produce peripheral edema.^{12, 40, 52} Mende⁵² noted that if the escape of blood from an extremity was prevented, edema could be demonstrated when the volume of the leg was increased by 10 per cent. Drury and Jones¹² confirmed Mende's observation. Krogh, Landis and Turner⁴⁰ reported that fluid accumulates in the extracellular tissue spaces of man as the venous pressure becomes greater than 15 to 20 cm. of water.

Capillary Pressure. When the venous tension rises sufficiently during failure of the heart, one may visualize the pressure as distending the venules and capillaries with transudation of fluid into the tissues. That such a mechanism may indeed operate to foster edema was suggested by the experiments of Starling fifty years ago.^{72, 73} His concept taught that two factors—the hydrostatic venular and capillary pressure and the colloid osmotic tension of the plasma oppose each other constantly. By this mechanism fluid is held in abeyance between the fine blood vessels and the extracellular tissue spaces. Should the hydrostatic pressure exceed that of colloid osmotic force, transudation of fluid into the tissues occurs. Conversely, elevation of colloid osmotic pressure permits fluid to leave the tissue spaces and enter the circulation. Such a concept has dominated the thinking of clinicians for many years.

Some of the studies, using crude methods, failed to show any correlation between venous and capillary pressure.⁵ Landis,⁴³ however, studied the capillary pressure in normal subjects by a micromethod of cannulating capillaries. The inflation of pneumatic cuffs applied to the extremity produced a rise of capillary pressure corresponding to the rise in venous pressure. Fahr and Ershler,^{15, 16} employing Landis' technic, studied the pressure in the capillaries of the skin in

patients with predominant right ventricular failure. (Table 1.) The mean colloid osmotic pressure in this group of patients was 21 to 22 mm. Hg. In their studies, the venous capillary pressure was higher than the colloid osmotic pressure in all but one

failure.^{14,31,58,61,66,78} Under such conditions the lowered osmotic tension is in synergism with elevated capillary pressure to provoke augmented transudation. Several factors appear to contribute to a decrease in plasma protein during heart failure: (1) in-

TABLE I

During Heart Failure					After Compensation			
Case Number	Venous Pressure*	Capillary Pressure*			Venous Pressure*	Capillary Pressure*		
		Arteriolar Limb	Summit of Loop	Venous Limb		Arteriolar Limb	Summit of Loop	Venous Limb
1	12	25	5	30	18	12
2	10	35				
3	24	31				
4	10	25				
5	27	35				
6	25	..	30	18	24
7	30	15
8	20	..	35	24	11

* All measurements were in mm. Hg.

instance (Case 8). Since it is known that under normal conditions filtration occurs only from the arterial limb of a capillary loop,⁴³ the elevated venous capillary tension in these observations indicated that filtration occurred along the entire capillary loop. Fahr and Ershler concluded that the factor of increased capillary pressure satisfactorily explained the formation of peripheral edema in congestive heart failure.

The evidence that increased pressure within the capillary system in heart failure may force fluid from the circulating stream into the tissues seems well founded. It is necessary then to examine the evidence for the opposing (colloid osmotic) force.

Plasma Proteins. It has been repeatedly emphasized that the plasma proteins, particularly the albumin fraction, constitute the principal osmotically active material in the blood.^{19,30,31} Under ordinary conditions these substances exert an osmotic tension of about 25 mm. Hg. Evidence indicates that the colloid osmotic pressure is frequently low in patients with cardiac

adequate protein intake; (2) deficient absorption from a congested intestinal mucosa; (3) excessive protein loss in the urine and in ascitic and pleural fluids and (4) faulty synthesis of protein by the liver.^{19,31,69} Although the plasma proteins may be low in some cases of chronic heart failure, hypoproteinemia is frequently absent.^{19,31} It appears that the depletion of plasma protein is rarely sufficient to be the sole factor in edema formation but quite probably it is accessory in some instances.

The Permeability of Capillaries. The early studies of edema formation in heart failure indicated that the integrity of the capillary wall is of considerable importance.^{6,70,71} Smirk⁷⁰ studied the problem in a group of normal subjects and in patients with congestive heart failure. Pneumatic cuffs were placed about the extremities; when these were inflated to a pressure equivalent to 20 cm. of water higher than the colloid osmotic pressure of the plasma, edema of the extremities occurred. The degree of volume increase of the extremities was

measured with a plethysmograph. He noted that a significantly greater rate of swelling occurred in the extremities of heart failure subjects. For instance, the average increase in hand volume expressed in cc. per 100 cc. of hand per five-hour period was 5.7 in normal subjects and 11.4 in patients with congestive heart failure. However, the possibility remains that the cardiac patients may have had occult edema when the experiment was performed; venous obstruction then may have brought the edema rapidly to a clinical level.

Several explanations have been offered for the capillary changes leading to increased permeability. Loeb⁴⁷ and others^{19,57} adduced evidence that venous stasis, accompanying venous hypertension, increases the permeability of capillary walls. Some observers^{6,19} have suggested that faulty nutrition of the capillary wall, resulting from slow blood flow, causes damage to the vessel. This idea is attractive but has been difficult to prove. Krogh³⁹ advanced the hypothesis that in certain conditions, capillary dilatation (under the impact of venous engorgement from heart failure⁵⁷) leads to an increase in capillary permeability. This possibility was not borne out by the studies of Landis.⁴¹ Furthermore, Fahr and Ershler^{15,16} found that capillaries in patients with heart failure could be twice their normal size without edema formation.

Of particular interest concerning the pathogenesis of capillary changes are the outstanding experiments of Landis.⁴² Using microcannulization technics, he showed that the capillaries of the frog mesentery are rendered permeable to fluid and protein by oxygen lack. Such a "protein leak" by the capillaries was demonstrable within a matter of minutes after oxygen deprivation. The process was found to be readily reversible unless capillary damage was allowed to become severe. This observation suggested that anoxemia may form the basis for increased capillary permeability during heart failure. Altschule¹ maintained that a decrease in cardiac output leads to anoxemia and that low oxygen saturation of

the blood causes an increase in capillary permeability. Clinical observations supporting this hypothesis indicate that some edematous cardiac patients respond to the administration of oxygen with profuse diuresis only to regain edema when deprived of oxygen.^{3,63} Indeed, Drinker¹⁰ has emphasized the rôle of anoxemia of pulmonary capillaries in producing pulmonary edema in myocardial decompensation as well as in other conditions.

The rôle of anoxemia in the production of edema has been disputed by several workers.^{15,16,81} For example, in congenital heart disease of the cyanotic type, a marked reduction in the oxygen content of the blood may be present for years without the occurrence of edema.¹⁶ Furthermore, patients with cardiac decompensation frequently develop edema without a marked reduction of oxygen content of the blood.¹⁶

It has been argued that if increased capillary permeability is present, the edema fluid will contain large amounts of protein.⁸¹ Repeated investigations^{8,83} have shown that the protein content of cardiac edema fluid is low, usually less than 0.5 Gm. per cent. Warren and Stead⁸³ measured the protein content of edema fluid in cardiac patients before and after compensation and found no significant change. The low protein content of edema fluid in patients with heart failure, with severe emphysema and with longstanding anoxemia, has been cited as evidence that pronounced oxygen desaturation of the blood does not increase capillary permeability.⁸¹ None of these data, however, are conclusive. A large amount of protein may pass into the extracellular fluid and the protein concentration may conceivably remain constant if enough water also enters the tissue spaces.

The evidence regarding the rôle of capillary permeability in the pathogenesis of cardiac edema is at the present time both inconclusive and conflicting.

Lymph Flow. Early workers suggested that lymphatic return is increased in the course of cardiac failure.⁷ However, McMaster³¹ has reported the occurrence of

lymphatic stasis in cardiac patients. He suggested that retardation in the flow of lymph resulted from dilatation and valvular incompetence of the lymphatic vessels themselves. In the same connection, it must be considered that the lymph channels empty into the systemic veins and that an elevation of venous pressure may impair the escape of lymph from these channels.³⁰ From the experimental evidence at hand, however, it appears that lymphatic obstruction in cardiac patients is the least important of these many possible factors concerned in edema formation. The extracellular fluid resulting from lymphatic blockage is high in protein content.¹¹ The finding of lowered protein content of cardiac edema fluid, therefore, constitutes the main body of evidence against the importance of lymphatic obstruction in circulatory failure.

Endocrine Factors. Endocrine imbalance as a cause of salt retention should be considered although its importance in edema formation is still not clear. Evidence that salt retention is directly correlated with an increase in certain steroid hormones was found by Thorn and Emerson.⁷⁹ They demonstrated a premenstrual retention of salt and water. During and following the menstrual period salt was excreted in excessive amounts and water was lost with it.

Adrenocortical hormones have been known for many years to be concerned with salt metabolism of the kidney. According to Raab,⁵⁹ certain adrenocortical hormones are greatly increased during congestive heart failure. His studies indicate the need for a thorough investigation of the effect of hormones secreted by the adrenal cortex in heart failure.

Since some patients with cardiac insufficiency and edema failed to have a normal diuretic response to ingestion of water, Fremont-Smith^{21,22} postulated an increased secretion of the antidiuretic factor by the posterior pituitary gland. Recent studies by Ralli et al.⁶⁰ on the mechanism of ascites in cirrhosis of the liver offer another explanation for the apparent increase in the antidiuretic factor. The amount of the anti-

diuretic factor normally inactivated by the liver is greatly decreased as a result of impaired liver function.⁶⁰ In cases of cardiac decompensation with long-standing congestion of the liver, the antidiuretic factor may not be destroyed and, consequently, may play a part in water retention. Investigation of the rôle of the antidiuretic factor in the pathogenesis of cardiac edema may prove productive.

SUMMARY AND CONCLUSIONS

1. Evidence concerning the rôle of the principal factors thought to be involved in the pathogenesis of peripheral cardiac edema has been presented.

2. Studies of cardiac output do not show a consistent decrease in this function; however, the data indicate a definite trend toward a low cardiac output during congestive heart failure.

3. There is considerable evidence that renal function is impaired during cardiac decompensation so that salt and water are retained by the kidneys. Sodium chloride and water retention is accompanied by abnormal water storage in the extracellular tissues and thence edema formation. Glomerular filtration and renal blood flow have been reported to be markedly decreased during heart failure; decreased glomerular filtration has been offered as a likely mechanism for salt retention. Renin, which has been found to be increased in renal venous blood of patients with cardiac failure, may be causally related to functional changes in the kidney but this relationship is not clear.

4. One of the most interesting features of the mechanism of edema formation is the problem of the pathogenesis of venous hypertension. The conceptions of "backward failure" and "forward failure" have been contrasted in some detail. At present, the evidence does not permit of a conclusive answer to the cause of elevated venous tension in heart failure.

5. When the venous pressure is elevated during cardiac decompensation, it plays a part in edema formation. An increase in capillary pressure is present and transuda-

tion of fluid into the extracellular tissues occurs.

6. Plasma proteins are sometimes low in patients with cardiac failure. When they are below a certain critical level, the lowered osmotic pressure may act as an accessory factor in the formation of edema.

7. It has been suggested that adrenocortical and posterior pituitary function may be disturbed during congestive heart failure but there is, as yet, no satisfactory evidence in support of this hypothesis.

8. The evidence is insufficient to warrant the conclusion that increased capillary permeability and partial lymphatic obstruction are major considerations in the pathogenesis of edema.

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Seminars on Thromboembolism

Use of Anticoagulants in the Treatment of Heart Disease*

With Special Reference to Coronary Thrombosis, Rheumatic Heart Disease with Thromboembolic Complications and Subacute Bacterial Endocarditis

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INVESTIGATION regarding the possible value of anticoagulants in the treatment of thromboembolic phenomena continues to appear logical and, indeed, imperative because of the following facts:

1. Thromboembolic phenomena cause the terminal fatal episode in the lives of more persons over fifty than any other pathologic mechanism.

2. A large percentage of these patients suffering from thrombi or emboli in the vessels of the brain, the heart, the kidneys, the legs, or elsewhere, do not or would not die from the effects of the original thrombus or embolus. Death results far more frequently from subsequent developments including: (a) propagation of the thrombus to block off additional arteries or veins which are strategically located so that they interfere with the vital function of the organ supplied; (b) the dislodging of emboli from the original thrombus which, when transported by the blood currents, lodge at critical points interfering with the blood flow and producing serious disturbances of the local tissues, or, in the event of emboli of sufficient size lodging in the heart, the pulmonary or the cerebral circuit, producing sudden death; (c) the development of secondary thrombi which may in turn give

off emboli. Examples of this type of process are represented by mural thrombi with coronary infarction and thrombi in the veins of the legs upon prolonged bed rest.

3. Experience has demonstrated that if a patient survives a first attack of thrombosis, or a first embolus, or indeed a subsequent attack, he may live for many months or even years. It is, therefore, incumbent upon us to do everything in our power to bring about survival through each individual attack.

4. Interruption of the thromboembolic process presents a logical approach to the problem. Our former methods of treatment of these thromboembolic phenomena have never been aimed at modifying the fundamental process involved. Frequently, as in the instances of coronary thrombosis or auricular fibrillation with heart failure, the combination of complete rest, restriction of fluids, sedation and mercurial diuretics have all encouraged further thrombosis either in the vessels, the chambers of the heart or in the veins elsewhere.¹ The effects of the xanthines, especially aminophylline^{2,3} and digitalins⁴ have been challenged in this regard. Work in our laboratory and elsewhere seems to exonerate aminophylline. As much as 1.8 Gm. given daily has failed to change

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the prothrombin time even while producing toxic phenomena. Frequently penicillin is used in the presence of thromboembolic episodes. It has recently been shown to increase markedly the thrombosing tendency both as to rapidity of formation and the firmness of the clot.^{5,6} This apparently holds also for streptomycin.⁷

5. It has seemed, therefore, that serious study must be given this problem. Fortunately, two agents are available, either of which apparently can interrupt the thromboembolic process under certain favorable conditions. It is the purpose of this article, therefore, to review the present status of the use of these substances, heparin and dicumarol, particularly in reference to diseases affecting the heart.

The era of intensive study with anticoagulants really began in 1916 when J. McLean,⁸ a student of William H. Howell, discovered heparin as a by-product of another investigation. Its anticoagulant properties were recognized with the initial experiment, and from that time forth Howell and other investigators have carried on many studies regarding the properties of this substance.⁹ As early as April 7, 1917, Howell, in a Harvey Lecture,¹⁰ expressed the hope that this or a related substance would find "a suitable application in experimental work, and possibly in the therapeutic treatment of disorders of coagulation." Early preparations, however, were not satisfactory for therapeutic use in man. Considerable work was carried on in the laboratories at John Hopkins^{11,12} and also at the Connaught Laboratories at the University of Toronto under Best.^{13,16} Later investigators, including Jorpes,^{17,18,19} continued investigations at the Karolinska Institut of Stockholm. Details of the discovery and the chemistry of heparin have recently been reviewed by Jorpes in his monograph on this subject.²⁰

A provisional international heparin standard was defined by the Department of

Biological Standards of the National Institute for Medical Research in London in November, 1942. A water-free sodium salt of heparin obtained from a "crystalline barium salt," supplied by the Connaught Laboratories of the University of Toronto, was selected as standard. It contained 130 Toronto Units per mg., thus approximating the strength of the strongest sodium salts of heparin from ox liver, or 160 per cent of the strength of the Swedish standard heparin.²¹ This difference in strength between the heparin prepared on the basis of the International Standard (which is that commonly used in this country) and the heparin prepared on the basis of the Swedish Standard must be borne in mind when interpreting the reports on the use of heparin in the Swedish literature. In other words, in terms of milligrams, the dose of heparin utilized in Sweden today averages approximately one-third or more higher than that necessary to produce the same therapeutic effects in terms of the heparin used in this country. This is frequently not realized by American physicians and may, if neglected, result in some unfortunate complications.

The exact mechanism of the action of heparin is not clearly understood. It appears that the activity of heparin is dependent on, or at least accentuated by, the presence of the serum proteins, especially a fraction of the serum albumins, and that it takes place largely on the prothrombin rather than on the activated thrombin. It is not clear whether this reaction is direct or indirect. A prominent feature of the reaction mechanism of heparin is the mutually neutralizing effect of heparin and thrombokinase. Some studies have been carried out on the significance of electric charges on the heparin effect. It has a high molecular weight and carries an exceptionally large surface charge, apparently the largest of all the organic compounds of the animal body. The strongest preparations consist of up to no less than 45 per cent sulfuric acid. The strongest

compounds of a similar nature hitherto known, "the nucleic acids," contain only 25 per cent of phosphoric acid. The anti-coagulant activity apparently increases with increasing sulfur content. Jorpes concludes that the increase in sulfur causes a greater increase in activity if introduced into the highly esterified samples, thus indicating that it is the abundance of biontic charges that makes the polysaccharide an anticoagulant.²⁰ Jorpes and his co-workers have demonstrated that the source of the formation of heparin, or at least its storage in the body, is to be found in the Ehrlich mast cells or heparinocytes which are found along the sides of the minute vessels, probably throughout the body, but in higher concentration in the subcutaneous and lung tissues.²⁰ Free and active exchange of fluid through the walls of the capillaries appears to be the means by which heparin is carried from these cells into the lumina of the vessels.²² A method of administration of additional heparin for clinical purposes will be described in detail later in this paper.

The second anticoagulant of great importance was described, isolated and synthesized by Link and his co-workers in a now historic series of studies at the University of Wisconsin.²²⁻²⁶ This preparation is known as dicumarol (3,3'-methylene-bis-(4-hydroxycoumarin)). It was first isolated from spoiled sweet clover and later synthesized from coal tar derivatives and has been shown to have a definite anticoagulant property. The exact mechanism of its action, like that of heparin, is not entirely established at this time but it is believed to be on the basis of an inhibition of the production of prothrombin by the liver. Shortly after the description of dicumarol and its chemical and anticoagulant properties by Link and his co-workers, three groups, Bingham, Meyer and Pohle²⁷ of the University of Wisconsin, Butt, Allen and Bollman^{28,29} of the Mayo Clinic, and Prandoni and Wright^{30,31}

of New York, undertook clinical investigations of the use of dicumarol in human beings, especially as it related to thrombophlebitis. Since that time it has been conclusively demonstrated by the work of these authors and others, notably Barker³² of the Mayo Clinic in this country, and Swedish investigators including Bruzellius³³ and Ziliacus,³⁴ that dicumarol exerts a favorable effect on the course of thrombophlebitis and the thromboembolic complications of that group of diseases. It has also been demonstrated to be of great value as a prophylactic measure in the prevention of postoperative emboli and thrombophlebitis.

The action, as indicated above, is not completely clear, but the following factors apparently play a part: (1) A decrease in the prothrombin activity. (2) A prolongation of the coagulation time. This factor is not always clearly demonstrated by the use of the Lee-White method for the study of coagulation time, but by using lusteroid tubes and paraffin-lined tubes, Kadish³⁵ and Vander Meer, Newman and Wright³⁶ have demonstrated that there is a prolongation of the coagulation time in dicumarolized patients. (3) A decrease in the thrombosing tendency has been demonstrated in various forms of neutral vascular tubing.³⁷ (4) There is a marked decrease in the thrombosing tendency following sodium morrhuate injections in dicumarolized patients.³⁷ (5) There is some evidence which suggests a decrease in the adhesiveness of platelets in the presence of dicumarol.³⁷ (6) There is evidence accumulating which suggests an increase in the antithrombin components or activity in the blood in dicumarolized patients.³⁷

The effects of heparin in terms of therapeutic results are very similar to those of dicumarol except that heparin acts more rapidly and therefore may be a valuable aid in the treatment of patients in whom rapid results are desired. Heparin is some-

what more difficult to administer in that it requires either continuous intravenous injections or a number of intramuscular or intravenous injections per day, or lastly it may be used with a retarding base, such as the Pitkin menstruum. When injected subcutaneously or intramuscularly the original preparations in the Pitkin menstruum produced pain and other local and general side effects. More recent modifications of these preparations are less objectionable in these regards but are still quite painful. We have not as yet had the opportunity of studying the other by-effects in detail.

Dicumarol is slower to act than heparin, requiring approximately thirty-six to forty-eight hours to manifest its activity, but since it is given orally it is easier to administer. Apart from the risk of hemorrhage from overdosage, it does not customarily produce any untoward effects such as digestive disturbances or reactions of hypersensitivity. There have been no definite examples of either of these latter reactions attributable to the drug in more than 800 patients treated with dicumarol under the author's observation. The use of dicumarol is accompanied by the difficulties inherent in the present prothrombin tests. Even the most sensitive coagulation time tests^{35,36} do not follow the prothrombin activity closely enough to be satisfactory for the control of dicumarol therapy; therefore, prothrombin activity tests must be used. The methods available today are not suitable for use except by a skilled technician and certainly the patient cannot control his own dosage. At the present writing the major obstacle preventing widespread use of dicumarol is the lack of a simple but accurate test for the determination of prothrombin activity in man.

TECHNIC FOR CLINICAL ADMINISTRATION OF DICUMAROL

The following routine for the administration of dicumarol has been found to be therapeutic

and safe. Having made certain that there are no contraindications to its use such as recent hemorrhage, blood dyscrasias with bleeding tendencies, active ulcers, hemorrhagic ulcerative colitis, etc., and with the first prothrombin time within normal range, 300 mg. of dicumarol is given in a single dose. Each morning the prothrombin time is determined and the dose for that day is decided upon after the result of the test has been received. Either 200 mg. or 100 mg. is given daily until a prothrombin time of 30 seconds is reached after which 100 mg. is given daily until the prothrombin time equals 35 seconds or more. Thereafter no dicumarol is given until the prothrombin time returns to under 30 seconds when again 100 or 200 mg. are given until a level of 35 seconds or more is reached. The objective should be to keep the blood at the therapeutic level of 30 to 50 seconds during active hospital treatment, and between 25 and 35 seconds during ambulatory treatment. If the prothrombin time rises to 60 seconds or more, or if hemorrhagic manifestations occur in the skin, mucous membranes, urine or stool, dicumarol is discontinued and vitamin K is given intravenously, 64 to 72 mg. once and repeated in four hours. Usually this will suffice to reduce the prothrombin time to safe limits within twelve to twenty-four hours; if not, fresh whole blood transfusions, one or two of 300 to 500 cc. each, will solve this problem. In 800 cases we have not had a death from dicumarol bleeding with the doubtful exception of one complicated case described later in this paper. Transfusions have been found necessary in only two of the last 200 patients treated.

IF HEPARIN IS TO BE USED, THE FOLLOWING STANDARDIZED PROCEDURES FOR THE USE OF HEPARIN ARE SUGGESTED

1. *Intermittent Dose Method.* (1) An initial clotting time of the whole blood in glass tubes should be performed before heparin is given. We recommend the Lee-White modification of the Howell method which, although crude, still appears to be the most practical test. It is performed as follows:* "One ml. of blood is withdrawn from the arm vein, using a small all-

* *A m. J. M. Sc.*, 145: 495, 1913.

glass syringe. The time at which the blood is drawn is noted. The needle is removed and the syringe then emptied into a small glass tube (Widal tube) about 8 mm. in diameter, which has previously been rinsed out with physiologic saline solution (.85 per cent). The tube is rotated endwise (tilted) every 30 seconds and that point at which the blood no longer flows from its position, but maintains its surface contour when inverted, is taken as the endpoint. Care must be used to exclude air bubbles, as they tend to accelerate coagulation . . . If the test is done at room temperature (65°–90°F.), the error, although present, is within one minute and may be neglected . . . Normal coagulation time is 6½ minutes (5–8 minutes).” At present coagulation times should be done in glass tubes. In extensive tests at The New York Hospital on the clotting times of whole blood in paraffin-lined and lusteroid tubes, in untreated as well as treated patients, we have observed a wide range of variation in the clotting times in paraffin-lined and lusteroid tubes. This makes their use unsuitable for this type of study and they cannot be recommended at present. Further studies are being carried out.*

2. Fifty mg. of heparin in 50 to 100 ml. of physiologic saline are then given slowly by vein.

3. Clotting times should be done fifteen minutes and two and one-half hours after the administration of heparin. If the clotting time at two and one-half hours falls below fifteen minutes, give 75 mg. of heparin for subsequent doses. After a few trial studies the selected safe therapeutic dosage may be continued without repeating the clotting times routinely. The check of one series each day is a safety factor.

4. The dosage schedule may vary from patient to patient according to the clotting times. In general, injections of 50 to 75 mg. of heparin are given every three or four hours and are continued for two days. (This is the method used by the Swedish workers in a large series of cases of thrombophlebitis. As previously mentioned, the dosage recommended by them should not be used in this country since the temporary International Standard for heparin,

used in the United States, is 160 per cent of the strength of the Swedish standard heparin.)

5. The dicumarol dosage plan is the same whether or not heparin is used and 300 mg. should be given concurrently with the first dose of heparin. Prothrombin times should be done every day on blood taken just *before* a dose of heparin is due, since large amounts of heparin in the circulating blood may affect the prothrombin determination.

II. *Continuous Intravenous Drip Method.* Some physicians may prefer the continuous intravenous method to the intermittent injection method. Accurate measurement of the prothrombin time to determine dicumarol dosage can be accomplished with this method only by slowing the drip from 5 to 8 drops per minute because the heparin interferes with the coagulation of the plasma used in the test. (It has not been proven that heparin has no antiprothrombin action.²⁰) If the continuous intravenous method is used, it is recommended that 300 mg. of heparin be put in 1,000 ml. of 5 per cent glucose and allowed to run into the vein at approximately 25 drops per minute for twenty-four hours. Clotting times should be done every two hours, otherwise trouble may be anticipated. The clotting time should be kept between 20 and 40 minutes. The total daily dosage necessary for this may vary considerably. The infusion needle should be firmly fixed in place. The veins of the backs of the hands or dorsal surfaces of the feet have been found to be the most satisfactory. Heparin given in this fashion may usually be discontinued after from twenty-four to forty-eight hours. Three hundred mg. of dicumarol may be given the first day. Four hours after the heparin infusion has been stopped, blood should be drawn for the prothrombin test and dicumarol dosage determined thereafter accordingly.

III. Due to local pain and other side effects, the original experimental preparations in the Pitkin menstruum were not suitable for general use. Even the more recent preparations are very painful.

TECHNIC FOR PROTHROMBIN ACTIVITY DETERMINATIONS

Most workers have used either the Quick test²² or the Link-Shapiro modification of the Quick

* VANDER MEER, R., NEWMAN, A. and WRIGHT, I. S. Unpublished data.

test^{24,39,40} for determining the plasma prothrombin. The Link-Shapiro modification of the Quick test which has been found to be satisfactory is performed in our laboratory as follows:

The reagents used are:

(1) 0.1 M sodium oxalate, prepared by dissolving 13.4 Gm. of anhydrous, reagent grade sodium oxalate in 1,000 ml. of distilled water; (2) 0.85 per cent sodium chloride, prepared by dissolving 8.5 Gm. of reagent grade sodium chloride in 1,000 ml. of distilled water; (3) 0.025 M calcium chloride, prepared by dissolving 2.77 Gm. of anhydrous, reagent grade calcium chloride in 1,000 ml. of distilled water; and (4) thromboplastin-calcium chloride mixture, prepared as follows: 2.5 ml. of 0.85 per cent sodium chloride is added to 50 mg. Maltine thromboplastin in a small centrifuge tube. It is stirred until a uniform suspension is obtained and the suspension is then kept (with constant stirring) at 54°–55°C. in a water bath for ten minutes. When the suspension has been cooled to 25°–26°C., 2.5 ml. of 0.025 M calcium chloride solution is added and the mixture stirred for four minutes. After centrifugation at 1,700 r.p.m. for four minutes, the tube is removed from the centrifuge, taking care not to stir up the packed sediment, and the slightly turbid supernatant fluid is pipetted off to be used in the determination. (Note: Ampules of thromboplastin should be stored in the icebox.)

The necessary apparatus includes:

(1) A 37.5°C. constant temperature water bath (Machlett No. 84–410 metal constant temperature water bath, or A.H.T. No. 9925-A glass constant temperature water bath); (2) 100 by 12 mm. test tubes; (3) copper test tube racks (Army medical type to hold 100 by 12 mm. test tubes); (4) stopwatch; (5) Folin-Wu micro sugar pipettes (Normax), graduated to contain 0.1 and 0.2 ml.; and (6) Kahn viewer (if the Machlette No. A84–410 type water bath is used).

In performing the test, blood samples are taken by mixing 4.5 ml. blood quickly with 0.5 ml. of 0.1 M sodium oxalate. The oxalated blood is centrifuged at 1,700 r.p.m. for ten minutes and the clear plasma is transferred with a pipette to a test tube. Clotting time

should be determined at once, but if stored in a refrigerator the plasma will remain stable for several hours. If prothrombin times are to be done on 12.5 per cent diluted plasma as well as on whole plasma, such a dilution can be made in another 100 by 12 mm. tube by diluting 0.1 ml. of whole plasma with 0.7 ml. of 0.85 per cent saline. This should be mixed by tapping the lower end of the tube.

Two tenths ml. portions of thromboplastin-calcium chloride suspension are transferred into 100 by 12 mm. test tubes with a 0.2 ml. micro blood sugar pipette and these tubes are placed in a rack along with the test tubes containing whole plasma or its dilution. The rack is then placed in a 37.5°C. constant temperature water bath. When the contents of the tubes have reached the bath temperature (usually 60 seconds), 0.1 ml. of whole or diluted plasma is transferred with a micro blood sugar pipette to a tube containing 0.2 ml. of thromboplastin-calcium chloride suspension. The plasma is quickly blown into the thromboplastin mixture while, at the same time, the stopwatch is started. The tube is tapped sharply to mix the solutions and a small nichrome wire stirrer is introduced to stir the solution at such a rate that the wire sweeps across the test tube from one side to the other two times per second. The process of stirring may take place outside of the water bath and viewed under the magnifying glass of a Kahn viewer. The end point, which is the formation of a fibrin clot, is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer, thus bringing to view a clear area. The clot is usually turbid since the calcium oxalate formed upon calcifying the oxalated plasma is enmeshed in the clot. The prothrombin clotting time is the time in seconds required to form a clot; normal standards are for whole plasma, 13 to 17 seconds; for 12.5 per cent diluted plasma, 35 to 42 seconds.

If a constant temperature water bath with glass walls is used, the clot formation can be viewed through the glass walls of the bath and a Kahn viewer is not essential. However, in our laboratory a Kahn viewer is preferred because thin clots, such as those obtained with 12.5 per cent diluted plasma, are obtained easily and quickly.

Findings resulting from this test are reported in terms of seconds or they may be translated into per cent of prothrombin activity. The normal results with whole plasma fall within a range of from 13 to 17 seconds. Slight therapeutic effectiveness may begin in some patients at approximately 23 to 25 seconds and become increasingly active as the time is prolonged. Thirty seconds and 35 seconds are key levels in regard to dosage. We endeavor to maintain a level of between 30 and 50 seconds to get maximum therapeutic effects without toxicity. Some workers, including Barker,³² believe that reports of these tests should be rendered in terms of percentage of prothrombin activity of normal plasma. When and if this can be standardized by the workers in this field it may be desirable, because it permits a correction for the use of thromboplastin of various strengths. At present, however, there are at least three different methods of setting up such curves in use in different institutions in this country. Therefore, reporting in percentage under these conditions may result in misinterpretation by other workers. The most correct technic uses a curve produced as the result of the dilution of normal plasma with prothrombin-free plasma so that 90 per cent, 80 per cent, etc., down to 10 per cent solutions of normal plasma are obtained and prothrombin tests performed on these various diluted samples. A curve can thus be plotted which will indicate prothrombin times for various percentage levels of prothrombin deficiency. This is a logarithmic curve, not a straight line. For example, the first few seconds' increase in the prothrombin time indicates a great decrease in the prothrombin percentage of normal. When the deficiency becomes marked, many seconds' increase may mean a difference of only a few per cent in the concentration of prothrombin. As Barker points out, "by plotting a dilution curve as above outlined, any worker using a thromboplastin of unknown potency can determine a set of prothrombin times for that thromboplastic substance which indicate various percentages of prothrombin deficiency and, if certain prothrombin percentages are considered important levels, he can easily determine their equivalents in prothrombin times." In order to continue this it is necessary

either to use only new thromboplastins which give identical results with the old, or to run relatively large samplings from so-called normals to establish a new curve with each new batch of thromboplastin.

The establishment of such a curve does not eliminate factors of error which have occurred in the prothrombin determinations and, in fact, it may actually magnify them. At present, following the technic of Russ, we are using Lyovac (dried plasma) prepared for this purpose as our standard control. It is used in the dilution of 12.5 per cent against the plasma of a similar dilution and gives standard results for that dilution of approximately 35 to 40 seconds.^{41,42}

A more serious problem, pointed out above, lies in the use by certain institutions at present of straight curves. In other words, if the normal control for whole plasma is 15 seconds, and the result of the patient's test is 30 seconds, this is considered to be 50 per cent of normal, a figure far different from that obtained on the logarithmic curve above described. A third technic which is unjustified has been found in use in certain institutions where, instead of 50 per cent, the same figures, namely, 15 per cent for the normal standard and 30 per cent for the patient, would be interpreted as 200 per cent. This may give rise to serious misunderstandings and at present appears to be safeguarded against by the use of reference to seconds and by standardizing the basic technic to the greatest degree possible.

Studies have been carried on in our laboratory at The New York Hospital regarding the effects of food and exercise on prothrombin times.⁴³ These studies were undertaken to investigate: (1) The daily variation in prothrombin activity of normal individuals; (2) to determine if the time of day that blood samples were taken affected the prothrombin activity; (3) to ascertain the effect of exercise on prothrombin activity and (4) to study the effect of high cholesterol intake on the prothrombin determination. In these studies we used the one step method of Quick. Plasma prothrombin times were measured on both whole (100 per cent) and diluted (12.5 per cent) plasma.

Diurnal prothrombin time determinations were investigated in twenty normal individuals

over a period of four to ten weeks. An average of 15.4 seconds (90 per cent of the values obtained are within the range 15.4 ± 1.5 seconds) was obtained as the prothrombin time of 625 determinations on whole plasma. The average prothrombin time in 627 determinations of 12.5 per cent plasma was 38.4 seconds (75 per cent of the values obtained are within range 38.4 ± 3 seconds).

In order to determine if the time of day had any effect on prothrombin activity, blood samples were taken before breakfast, before lunch and after lunch on nine different individuals over a period of three weeks. One hundred prothrombin determinations were made on blood samples taken before breakfast. The average prothrombin time of 100 per cent plasma was 15.0 seconds; that for 12.5 per cent plasma was 35.4 seconds. Before lunch the average value for 109 determinations was 15.1 seconds for 100 per cent plasma and 39.4 seconds for 12.5 per cent plasma. After lunch the average was 14.5 seconds for 100 per cent plasma and 37.5 seconds for 12.5 per cent plasma for 115 prothrombin determinations.

The effect of a short period of strenuous exercise on prothrombin activity was also studied in ten normal students. Blood samples were taken, and the students then ran down and up four flights of stairs, following which blood samples were taken again. Before exercise, thirty-five determinations were made. The average was 16.7 seconds and 39.9 seconds for 100 per cent and 12.5 per cent plasma, respectively. After exercise, an average of 16.6 seconds and 39.9 seconds on 100 per cent and 12.5 per cent plasma, respectively, was obtained in thirty-four determinations.

To ascertain if ingestion of a high cholesterol diet would affect the prothrombin activity, four normal individuals were given six eggs a day besides their usual meals and their prothrombin measured daily over a period of four weeks. The average of sixty-seven determinations on 100 per cent plasma and 12.5 per cent plasma was 16.1 seconds and 40.1 seconds, respectively.

The results of these studies indicate that although slight variations are obtained these are within the experimental error of the method. If any of these factors, such as the time of day that

blood samples are taken, exercise or high cholesterol intake, do affect the prothrombin activity, the changes are of minor significance. Therefore, prothrombin determinations may be made at various times of the day after exercise and in patients on a high cholesterol diet. They will be satisfactory for guiding dicumarol therapy unless other factors interfere.

CLINICAL EXPERIENCES WITH ANTICOAGULANTS IN THE TREATMENT OF THROMBOPHLEBITIS

The results following the use of dicumarol and heparin, given separately or in combination, in the treatment of thrombophlebitis have been so remarkable that investigation of the use of anticoagulants in other diseases is justified. Figures on large series reported by Barker and co-workers,³² Bruzelius,³³ Jorpes,²⁰ Zilliacus³⁴ and by our own group⁴⁴ clearly indicate that the use of anticoagulants constitutes the most important forward step in the treatment of thrombophlebitis. It is interesting that almost identical results were being obtained in Sweden and in this country although communication was markedly inhibited during the war years.

INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS OF MYOCARDIAL INFARCTION

The importance of thromboembolic complications of coronary thrombosis with myocardial infarction has long been recognized. In 1937, Blumer⁴⁵ reported 943 cases of myocardial infarction in 132 of which clinically detectable emboli or thrombi were found. Hellerstein and Martin⁴⁶ have recently reviewed the literature and have added 655 cases from later reports. The incidence of clinically detectable thromboembolic lesions for the entire group was 11.5 per cent. In their autopsy series of 160 cases of myocardial infarction, however, 73 (45 per cent) had a total of 111 peripheral thromboembolic episodes. These peripheral complications were a main or contributory

cause of death in 43 of the 160 cases. Master and his associates⁴⁷ have stated that in patients under fifty the most common cause of death associated with myocardial infarction is arterial embolism. Nay and Barnes⁴⁸ reported embolic or thrombotic complications in 37 of 100 consecutive cases of acute myocardial infarction encountered in the Mayo Clinic. In these thirty-seven patients there were a total of forty-eight thromboembolic complications, and these complications were an important contributing factor in the death of twelve patients.

ANIMAL STUDIES WITH ANTICOAGULANTS IN CORONARY THROMBOSIS AND MURAL THROMBI

The recognition of the occurrence of such thromboembolic complications of coronary thrombosis and other heart disease led early workers to speculate on the possibility of anticoagulant therapy in these conditions. Solandt and Best,⁴⁹ in 1938 reported experiments in which coronary thrombosis was produced by isolating the coronary artery and injecting sodium ricinoleate within the lumen. This material was kept in contact with the intima for five minutes and clamps on the vessel were then released. In almost every case in which no heparin was used thrombosis was present; whereas in the heparinized series this was almost never observed. Solandt, Nassim and Best⁵⁰ continued their studies with the production of cardiac mural thrombi, and the prevention of their formation by the administration of heparin. A technic was evolved by which large mural thrombi could be regularly produced in the lumen of the left ventricle. The endocardium of this cavity was injured by injecting sodium ricinoleate, and the myocardium was damaged by ligating the anterior descending branch of the left coronary artery. Without heparin there was rapid formation of a thrombus but none was seen in those experiments in which heparin

was given well before the injury was produced. The results of their experiments left no doubt that under certain experimental conditions the effect of heparin in preventing thrombosis could be readily demonstrated. Following these studies sporadic efforts were made to use heparin in the treatment of coronary thrombosis, but as far as is known no large well controlled series were run, largely because of the difficulties of continued heparinization. The question of increasing the hemorrhage in the intima was also raised, more as a theoretical than as a proven risk. Following the early clinical use of dicumarol a few patients with coronary thrombosis with myocardial infarction were treated with it. The author treated his first patient with thrombophlebitis in May, 1942.

CLINICAL EXPERIENCE WITH THE USE OF ANTICOAGULANTS FOR THE TREAT- MENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

It is difficult to evaluate the effectiveness of anticoagulant therapy in a particular patient who has suffered from an uncomplicated attack of coronary thrombosis in its early stages, since at present we are unable to predict with certainty which patient will have a rapid series of secondary episodes of thrombosis, which will have one or more embolic phenomena, and which patient will prove to have an uneventful recovery from the immediate attack. The patient who has had a series of episodes of thrombosis in different radicals of the coronary tree within a short period of time, and with evidence of multiple myocardial infarctions following these, or whose original thrombus propagates centrally thus blocking off additional branches of the same coronary artery and producing a much larger area of myocardial infarction, has an increasingly serious prognosis with each episode or extension. Once a

person has more than two episodes of thrombosis within a period of two or three weeks there is an increasing likelihood that further episodes will follow and the outlook is progressively poorer. In like manner, once a patient has developed a mural thrombus and has suffered one or more embolic phenomena, either pulmonary or peripheral, the prognosis is grave although some individuals do survive such episodes. It has been the lot of all cardiologists to care for many patients through such a course, helpless to prevent the repeated complications of thromboembolism and to avert death. In fact, as previously pointed out, the regimens which include complete rest, the rather free use of narcotics or other sedatives, and, when indicated, the use of mercurial diuretics, encourage the production of additional thrombosis, the very thing which is, in another sense, being combated. In spite of the difficulty of evaluating the results of such treatment in the individual case with coronary thrombosis, the significant results obtained in the study of thromboses of other types warranted an exhaustive study of this group of cases. In order to put the drug to the most difficult test first, a group of patients who were classified as the "complicated group" were selected on the basis of fulfilling one or more of the following criteria:^{53,54}

1. Patients who developed evidence that thrombi had formed in different areas of the coronary tree, or that the original thrombus had propagated. These conclusions were based on evidence either of multiple areas of myocardial infarction or a marked extension of the original area, with characteristic precordial pain, fever, leukocytosis and increased sedimentation rate, and accompanied by definitely confirmatory electrocardiographic findings.

2. Patients who suffered from repeated embolic phenomena either to pulmonary or other areas. (It was recognized that cer-

tain of the pulmonary emboli might have arisen in the extracardiac circulation; but following myocardial infarction, the percentage of pulmonary emboli is considerable, and from whatever source, repeated pulmonary emboli have an increasingly serious prognosis.)

3. Patients who developed evidence suggesting that factors one and two were both operative.

Experiences with forty-three such complicated cases and an additional thirty-three patients who had suffered from uncomplicated first or second attacks of coronary thrombosis, making a total of seventy-six patients, were reported in October, 1945, before the California Heart Association.* This series has continued to increase, but has recently been incorporated into a national study of this problem. The figures of this large study have not been completed as yet. Of the first forty-six complicated cases in the original series, forty-one patients ceased having their serial episodes as soon as they were under the effect of dicumarol; eleven died (24 per cent).⁵³ This mortality is the same as that for coronary thrombosis with myocardial infarction as a whole, but was less than the estimated mortality for these patients (60 per cent plus), who were selected because of the extreme seriousness of their condition. Eight of these died of cardiac failure secondary to their pretreated massive infarctions. Of the thirty-four uncomplicated patients treated, four died (12 per cent). This incidence is lower than the average rate (20 to 30 per cent). A few case histories illustrating the type of patients selected for this form of therapy may be considered to be of interest:

CASE 39. *Multiple thromboses within the coronary arteries with myocardial infarctions:* A fifty year old Army major developed a coronary thrombosis with anterior myocardial infarction. Twelve

* Stanford U. Medical College.

days later, he developed a posterior infarction. Nineteen days later, there was evidence of extension of the posterior infarction. This patient, therefore, was considered to be a complicated case of coronary thrombosis. There was evidence of thrombosis in several areas of the coronary tree and probably extension in one of the areas. At the time that he was seen by the author he was desperately ill, in an oxygen tent, gasping for breath, cyanotic and profusely sweating. His outlook appeared grave. Dicumarol was given for thirty days. There were no further episodes of extension. He made an uneventful recovery and was retired from the Army to return to his civilian home.

CASE 77. Coronary thrombosis, infarction, mural thrombus and peripheral emboli: A male, forty-six years of age, also an Army major, had suffered an anterior infarction. On the eighth day he developed an embolism to the right femoral artery; on the tenth day, an embolism to the left femoral artery; and on the twelfth day, a cerebral embolism. He, likewise, was in extremis when seen by the author. It is possible that the embolic phenomena to his legs really constituted a saddle embolus, but this was not clearly established. Despite the bad prognosis, he was started on dicumarol which was continued for thirty days. No further episodes of embolism occurred, and he made a very satisfactory recovery but had residual intermittent claudication of his right calf muscles upon walking three blocks.

CASE 78. Septal infarction, cerebral and peripheral emboli: A female, sixty-eight years of age, suffered from hypertension and diabetes of many years' duration, and also had gallbladder disease. She developed a septal myocardial infarction with auricular fibrillation. On the twenty-eighth day she had an embolism to the right femoral artery. On the thirty-first day she had a cerebral embolism which produced hemiparesis and aphasia. She became desperately ill. Dicumarol was started and continued for eighteen days. At that time it was necessary to stop it so that the leg which had meanwhile become necrotic and infected could be amputated. This was done four days after cessation of the dicumarol therapy. She had an uneventful recovery, including recovery of her speech,

and is alive at the time of this writing some fifteen months after the above episode. She still continues to have auricular fibrillation.

CASE 21. Pulmonary infarctions from a mural thrombus; death from heart failure: A male, forty-two years of age, developed an anterior infarction. On the sixth day he experienced pain in the right lateral chest followed by bloody sputum, and at the same time developed auricular fibrillation. The chest pain was believed to be due to a pulmonary embolism. This was confirmed by an episode on the seventh day with pain in the left base posteriorly. On the ninth day there was a repetition of this type of episode in the right middle lung field. Dicumarol therapy was started. No further emboli occurred. Nevertheless, the patient pursued a downhill course, and died on the thirtieth day, which was after twenty-one days of dicumarol therapy.

At autopsy, he was found to have generalized congestive failure. He had multiple pulmonary infarcts but none appeared to have occurred within two weeks. There was a thrombus in the right coronary artery blocking several branches. In this area the myocardium was necrotic, yellow, fatty and very soft. Attached to the endocardium at this site was an olive-shaped mural thrombus which appeared relatively recent, but was completely sealed over and very smooth. An examination of the patient's veins showed no other likely sources of emboli. It appeared probable that the mural thrombus, which at one time was propagating irregularly and capable of giving off emboli, had become sealed over and smooth following anticoagulant therapy. This could not be proven conclusively. Four additional similar mural thrombi have been seen in later autopsies of treated cases.

Numerous additional cases might be cited in each of the above classes.

PRELIMINARY CONCLUSIONS REGARDING THE USE OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

After three and one-half years of study involving eighty patients, the following conclusions seemed warranted:

Dicumarol had not aggravated the condition of any patient. It appeared physiologically sound to give anticoagulant therapy when there was a tendency for (1) propagation of the thrombus, (2) multiple thrombi to form in the coronary arteries or elsewhere and (3) when one or more emboli had occurred. Thromboembolic processes appeared to have been interrupted. There was no evidence that thrombi had been dissolved once they had formed. Progression of established infarctions did not appear to be interrupted by the use of dicumarol. The rate and rhythm of the heart was not directly affected by dicumarol. The risk of future attacks appeared unchanged after dicumarol had been discontinued.

In January, 1946, Nichol and Page⁵⁵ described their experiences with dicumarol therapy in acute coronary thrombosis, reporting results in fifty unselected attacks occurring in forty-four patients seen between June, 1943, and October, 1945. Eight of the fifty patients died, an immediate mortality rate of 16 per cent. It was noteworthy that all of the twenty-six patients who were treated for their first attack survived. In only one case was there clinical evidence of a pulmonary embolus and this patient had been given an inadequate dose of dicumarol. In six autopsied cases no mural thrombi, systemic or pulmonary embolic phenomena were found. In a recent personal communication, Nichol has informed the author of a patient who, having suffered three serious attacks of coronary thrombosis with myocardial infarction, has been on dicumarol therapy for more than forty months with no further attacks of coronary thrombosis and with no toxic effects of dicumarol. He did have one episode of severe bleeding from a peptic ulcer. In February, 1946, Peters, Guyther and Brambel⁵⁶ reported their experiences using dicumarol in acute coronary thrombosis, beginning in March, 1943. They compared

fifty dicumarolized patients with sixty non-dicumarolized patients, and reported the following results: In the group of sixty patients who did not receive dicumarol, there were seventeen with congestive failure who were given digitalis. Of these seventeen, nine or 53 per cent died, most of them as a result of embolism. In the group of patients receiving dicumarol, eight were given digitalis for congestive failure. One of these (12.5 per cent) died, apparently of renal complications. In the sixty patients receiving conventional treatment for coronary thrombosis, the incidence of clinical embolism was 16 per cent and the mortality rate was 20 per cent. By contrast, in the fifty patients receiving the conventional treatment plus dicumarol sufficient to maintain their plasma prothrombin activity at 35 to 50 per cent of normal, the incidence of clinical embolism was 2 per cent and the mortality rate was 4 per cent. They reported an increased clotting tendency as evidenced by a decrease in the prothrombin clotting time (12.5 per cent diluted plasma) in most of their patients with acute coronary thrombosis. They also concluded on the basis of figures mentioned above that digitalization for congestive failure in coronary thrombosis increases the incidence of thromboembolic phenomena and that this hazard may be nullified by dicumarolization of such patients. Parker and Barker⁵⁷ have recently reported fifty additional cases of myocardial infarction and have compared the results with 100 cases treated conventionally in the series of Nay and Barnes. They were as follows: deaths in the controls, 13 per cent—anticoagulant cases, 10 per cent; thromboembolic complications in the controls, 37 per cent—anticoagulant cases, 4 per cent. In addition to the above four groups of workers, a few individuals have reported isolated cases and small series of patients treated with dicumarol therapy.

All of the material presented thus far is open to the following criticisms:

1. The various series reported are too small to be statistically conclusive.
2. In no series have alternate cases been studied so that the selection of cases not treated with dicumarol may not be completely unbiased and they cannot therefore be accepted as absolutely valid controls.

PRESENT AND FUTURE STUDIES REGARDING
THE USE OF ANTICOAGULANTS IN
THE TREATMENT OF CORONARY
THROMBOSIS WITH MYOCARDIAL
INFARCTION

The American Heart Association has therefore established a Committee for the Evaluation of Anticoagulant Therapy in the Treatment of Coronary Thrombosis with Myocardial Infarction. The work of this committee has been subsidized by a grant from the U. S. Public Health Service. The work is being carried on actively in fifteen hospitals at present. All patients suffering from coronary thrombosis with myocardial infarction admitted on the participating services of these hospitals on odd days of the month receive anticoagulant therapy. Patients admitted on even days of the month do not receive it. Careful records are being compiled on master forms which are being forwarded to the central office of this study at The New York Hospital, where they are being subjected to statistical study and analysis. It is anticipated that from 800 to 1,000 cases will be studied. The results should be sufficiently large and statistically valid. The figures at present are encouraging, but it is too early to consider them as definitive or not subject to marked change with larger numbers. In some of these hospitals patients receive heparin during the first two days of treatment while the action of dicumarol is becoming effective. Further studies regarding the desirability of giving heparin immediately in all cases are being

planned. Particular attention to this phase of the study is being paid by Glueck and her co-workers⁵⁸ at Cincinnati, and the results to date have been favorable.

In an unpublished survey of 111 cases of myocardial infarction studied from 1932 to 1936 under the supervision of the Laboratories of Pathology, Bellevue Hospital and New York University College of Medicine, Graef⁵⁹ noted that myocardial lesions bore an inconstant relation to the state of coronary arteries. In ten cases (9 per cent) there was no gross or microscopic evidence of coronary occlusion, thrombotic or atherosclerotic occlusion. The great majority (91 per cent) had multiple occlusions of different sorts in one or both coronary arteries. Of the 101 cases with occlusion, sixty-three had thrombotic occlusion (always in the presence of arteriosclerosis) while the rest had atherosclerotic narrowings of various degrees. However, it was noted that in those with thrombotic lesions the thrombi were quite variable in estimated age when compared with the co-existing infarcts. In thirty cases with recent fresh infarction seventeen had fresh unorganized thrombi in coronary vessels supplying the affected area, while two had old organized thrombi. In the remaining eleven cases there were no thrombotic lesions; these had marked narrowing in one or more places in the coronary arterial tree. In fifty-three subjects with old myocardial infarcts twenty-five had old coronary thrombi while six had fresh thrombi.

It seems possible, therefore, that thrombosis may follow infarction due to coronary insufficiency, the myocardial fiber swelling and necrosis impeding capillary flow, leading to stasis in the nutrient artery or arterioles. Where arteriosclerosis pre-existed and produced narrowing, such stasis might then lead to local thrombosis.

These data suggest that in certain individuals who have lived through a prelimi-

nary myocardial infarction, there may be subsequent thrombosis with an increased area of infarction producing serious later effects or perhaps even death.

It is highly probable on the basis of many observations that most thrombi, however small, having once occurred, do tend to propagate during the early hours or even days of their existence. This may be minimized by immediate heparinization, following which dicumarol may be continued over a longer period of time. This problem will be studied further by the committee. Another investigation which should be undertaken is the follow-up observation of patients who have received anticoagulant therapy and have thus survived one attack. Their outlook for the future should be evaluated. A follow-up study should also be undertaken of individuals who can continue dicumarol therapy over a long period of time in order to determine whether their prognosis is thereby improved, as compared with individuals who are not able to continue long-term dicumarol therapy. These represent a few of the problems to be considered in the future.

USE OF ANTICOAGULANT THERAPY IN THE TREATMENT OF THE THROMBOEMBOLIC COMPLICATIONS OCCURRING WITH RHEUMATIC HEART DISEASE AND AURICULAR FIBRILLATION

Another challenging group of patients in whom intracardiac thrombosis is a very important problem are those who have suffered from rheumatic fever and years later develop auricular fibrillation and intracardiac thrombi. These thrombi then propagate and release emboli from time to time. Such a series is now under our observation.^{44,60} The study of this group of patients seemed worth while after observing the results of the use of anticoagulants in patients who had developed multiple emboli associated with auricular fibrillation secondary

to coronary thrombosis. We were further stimulated by Dr. Harvey Ewing, who referred the first patient for this specific purpose. Thirteen such patients have been treated and eleven are being followed at this time with continuous ambulatory treatment; one has died; another has taken the treatment too irregularly to allow any conclusions.

The following histories are given as examples of this type of patient and of the problems involved in their treatment.

E. S., a female, forty-seven years of age, had typhoid fever at three years of age, scarlet fever at four years and rheumatic fever at five years. Rheumatic heart disease was recognized during the sixth year. Chorea was diagnosed at six, ten and twelve years. Since the age of thirty-three her heart had been in a constant state of auricular fibrillation, and during these years she had taken digitalis almost constantly. In 1935, she had an embolus to the left groin and also a pulmonary embolus. In 1942, she had a left cerebral embolus which produced a right hemiplegia from which she made a complete recovery. During the years of 1943 to 1944, it was estimated that she had at least six emboli, which were apparently small, in various locations throughout her body. In December, 1945, she developed two emboli, one renal and one mesenteric. In January, 1946, she developed her thirteenth definite embolus which was pulmonary, and in September, 1946, her fourteenth embolus which was also pulmonary. On November 15, 1946, she became decompensated. Two days later, she developed a fifteenth embolus to the right arm. This produced coldness, blanching, loss of pulsation below the elbow and appeared to endanger the arm. On November 19th, she developed the sixteenth embolus which was to the left leg; on November 25th, a seventeenth to the right lung field; and on December 3rd, her eighteenth to the right lower quadrant of the abdomen, which produced shock, paralytic ileus and later blood in the stool. On December 3rd, she developed her nineteenth embolus, which was to the left leg, and on December 6th, her twentieth which

was to the left forearm and produced marked generalized shock. The patient was acutely ill. Her outlook appeared extremely serious.

On the day of her twentieth embolus, because of her desperate condition, she was started on anticoagulant therapy despite the blood in her stools, which was believed to be secondary to a mesenteric infarction. She received 52.5 mg. of heparin intravenously at 9:00 P.M., December 6th; 52.5 mg. at 1:00 A.M., December 7th, and 50 mg. at 6:15, December 7th. She was also given 300 mg. of dicumarol on December 6th, followed by daily doses of 200 mg., and thereafter was regulated in accordance with the schedule previously outlined in this paper. She was continued for one month on this regimen while in the hospital. Her average requirement of dicumarol was 100 mg. five times weekly.

She was discharged from the hospital on January 6th, having immediate cessation of her embolic phenomena and a completely uneventful course following the administration of anticoagulants. She has since continued to receive anticoagulant therapy while ambulatory. She has had several episodes of ecchymoses of mild degree. Her prothrombin time has in general been kept between 25 and 35 seconds, the highest having been 44 seconds. At present her average dose is approximately 50 mg. of dicumarol per day. No further embolic episodes have occurred. The patient's general condition is excellent. She is able to travel and does so freely and without difficulty whenever satisfactory prothrombin studies can be arranged. Her heart continues to be in a state of compensated auricular fibrillation.

M. T., a female, thirty years of age, had had scarlet fever at the age of thirteen. No diagnosis of frank rheumatic fever was ever made. In 1940, she began to develop episodes of rapid heart action with paroxysms of orthopnea. In 1946, she had her first recognized embolus. This was a cerebral embolism to the left side producing aphasia and numbness of the right arm and unconsciousness. She made a complete recovery from this. On December 29, 1946, she had an embolus to the right leg. On January 2, 1947, she developed auricular fibrillation and heart failure. She was then hospitalized. On January 7, 1947, she developed what was

apparently a splenic infarct; on January 9th, another left cerebral embolus; on January 10th, dicumarol was begun; and on January 11th she had a probable mesenteric embolus. On January 17th, she developed mild abdominal pain which might conceivably have been an embolus; this was not definite. The prothrombin time at that time was 32.7 seconds. On February 7th, she was discharged from the hospital for ambulatory treatment. Her average requirement is 400 mg. of dicumarol weekly. There have been no further emboli.

C. C., a female, forty-seven years of age, developed rheumatic fever with decompensation in 1932. In 1933, she had a second attack of rheumatic fever. In 1938, she had a period of decompensation. In 1941, she again developed decompensation with the first recognized auricular fibrillation and flutter. In October, 1941, she presented her first embolic episodes. Her first embolus was to the right brachial artery. She then developed either a saddle embolus or emboli to both femoral arteries. In January, 1942, a right middle cerebral embolus occurred. In April, 1942, emboli involved both kidneys, the right brachial artery, both femoral arteries, probably an artery in the base of the spine and definitely the right third finger. In September, 1942, she became decompensated again. In March, 1944, she had another episode of emboli to both kidneys. In April, 1945, she developed a myocardial infarction. In January, 1946, a fairly definite saddle embolus occurred from which she recovered remarkably. In March, 1946, she again became decompensated and this recurred in September, 1946. On September 23rd, she had a shower of emboli to the cerebrum and to the mesenteric and peripheral vessels. On October 5, 1946, she developed a pulmonary embolus with infarction.

On October 11, 1946, dicumarol was started. At that time she had a questionable thrombophlebitis which had largely but not completely subsided. It finally did subside. On November 20, 1946, she had pinkish sputum but no pain. There was considerable doubt whether this was due to a pulmonary embolus or not. The prothrombin time then was 24.1 seconds, which is below a definite therapeutic level. On November 26th, she was discharged from the hospital

having had dicumarol for forty-seven days during which time she had one questionable embolus. From that time until January 22nd she remained at home where she received no dicumarol and was in a state of persistent decompensation and fibrillation.

On January 22, 1947, she was readmitted to The New York Hospital with pulmonary and mesenteric emboli. On January 23rd, she had additional pulmonary and probably a splenic embolus. Dicumarol was again started. On January 25th, she had boring pain in the back opposite the left eleventh rib. There was no hemoptysis. There was some question as to whether this was an embolus or not. On February 7th, she was discharged from the hospital having had dicumarol for fifteen days. No further emboli occurred during that time. The patient returned to her home. No satisfactory arrangements could be made for continued anticoagulant therapy.

The patient remained in bed at home, receiving digitalis 0.1 Gm. daily, ammonium chloride 2.0 Gm., three times a day, and mercupurin injections twice weekly. There was persistent pain in the abdomen and right leg, also dyspnea and frequent attacks of vomiting, but no bleeding or hemoptysis. On March 17, 1947, she suffered severe pain down the right leg and severe occipital headache, and on the following day there was sharp pain in the left anterior chest with severe cough productive of rusty sputum and chills.

The patient was readmitted to The New York Hospital, her twelfth admission, on March 19, 1947. Physical examination upon entry revealed a temperature of 40.3°C., dyspnea and cyanosis, dullness to percussion at the right base and many râles upon auscultation of the left lower axilla and base posteriorly. The cardiac rhythm was grossly irregular, beats were frequently coupled and there were occasional runs of rapid, regular, rhythm. There was a systolic murmur in the tricuspid area and both systolic and diastolic murmurs over the aortic and mitral areas. A pulsating liver could be felt 7 cm. below the costal margin. There was a 1 plus ankle edema. Diagnoses upon entry were: (1) Rheumatic heart disease with enlarged heart, auricular fibrillation, mitral and aortic stenosis,

mitral and aortic insufficiency, tricuspid insufficiency, decompensated; (2) chronic passive congestion of the lungs and liver and hepatomegaly, possibly secondary to cardiac cirrhosis; (3) possible bacterial pneumonia; and (4) possible pulmonary infarct of recent origin.

The patient was treated with penicillin, 300,000 units twice a day for five days and 300,000 units daily for five days with deference and general improvement. Dicumarol was started on March 21, 1947, and the patient received 1,000 mg. in six days reaching a prothrombin level of 43.5 seconds on the eighth day. On March 27, 1947, the patient coughed up clots of blood and suffered very mild low substernal pain. Prothrombin time was 39.7 seconds and dicumarol was discontinued. On the next day the patient coughed up 100 cc. of fresh blood. Her prothrombin time was 43.5 seconds. Hykinone, 72 mg., was given intravenously and the hemoptyses subsequently decreased in amount. On April 1, 1947, the patient was still coughing up blood and, although no dicumarol had been given, the prothrombin time was 36.1 seconds. Vitamin K was given intravenously in a dose of 72 mg. On April 2nd, there was a hemoptysis of 300 cc. of blood, and the prothrombin time was 29.7 seconds; 72 mg. of vitamin K was injected intravenously and a blood transfusion of 500 cc. of whole blood was given. On the following day hemoptysis had decreased to about 50 cc. and the prothrombin time had fallen to 23.0 seconds. Respirations were rapid, 34 per minute, and râles were heard in all lung fields. On April 4, 1947, there was an episode of sudden and severe dyspnea. Breath sounds were diminished over the left chest. The pulse was 130 beats per minute and respirations were 36 per minute. A portable x-ray of the chest revealed hilar infiltration in the left lung with markings accentuated to the periphery. The prothrombin time was 19.0 seconds and there was no hemoptysis. The patient became progressively dyspneic and cyanotic and expired April 5, 1947.

Autopsy revealed the following pathological findings: There was advanced chronic rheumatic heart disease with stenosis and insufficiency of the mitral, aortic and tricuspid valves. The heart weighed 600 Gm. and was moderately

dilated and hypertrophied. There was thickening and fusion of the leaflets of the tricuspid valve (7.5 cm. circumference) and of the mitral valve (5.0 cm. circumference) with fusion, thickening and shortening of the chordae. The aortic cusps were thickened and the commissures were fused (circumference 6.5 cm). Beneath the aortic valve there was a pocket-like thickening of the endocardium. There was an old organized mural thrombus in the left atrium. There was an old infarct involving the apex and septum of the left ventricle and old infarcts of the spleen and kidneys. Despite the extensive scarring and thinning of the apex of the left ventricle and of the septum with aneurysmal bulging and fibrous pericardial adhesions over the area, no occluded vessel to the region was found.

There was advanced confluent lobular pneumonia with advanced chronic passive congestion, edema and partial collapse of the lungs, which weighed 1,570 Gm. There were firm, red, consolidated areas in the lower lobes and scattered similar areas elsewhere. A cast of clotted blood was found to occlude the left main bronchus and its major branches and there was a moderate amount of bloody mucoid material in the bronchi to both lungs. There was advanced chronic passive congestion, fatty degeneration and moderate cardiac cirrhosis of the liver, which weighed 1,600 Gm. and was moderately and finely nodular.

The possibility of influencing the prognosis of this patient favorably was believed from the beginning to be especially poor because no anticoagulant therapy could be arranged at home, and because the living conditions of this patient were never satisfactory for good care. The part dicumarol played in the production of the terminal hemorrhages is open to question but it must be seriously considered. This case is included to illustrate the difficulties which may prevent the use of anticoagulant therapy in the home care of some patients.

L. B., a female, thirty-eight years of age, developed rheumatic fever at four years of age. From then until she was twelve she had multiple attacks of rheumatic fever with the development of a heart lesion. In 1941, she developed auricular fibrillation, was found to have mitral stenosis

with cardiac decompensation. In February, 1946, she had a severe saddle embolus. She was then given heparin for two weeks. The embolus apparently divided, descending into both legs, and leaving her with occlusion of the major arteries above the knees bilaterally. In 1946, between February and June, she suffered six embolic episodes again involving her legs and also her abdomen and brain. In September, 1946, she had another embolus to her right foot, and again one to both legs. On November 2, 1946, she developed a cerebral embolus which produced dizziness, diplopia, slurring of speech, involuntary twitching of the right arm, occipital headaches and loss of convergence of the left eye. She was admitted to The New York Hospital on November 3rd and dicumarol was started at that time. She remained in the hospital for one month, since which time she has been ambulatory. Her average weekly requirement of dicumarol is somewhat higher than that of most patients. She needs approximately 900 mg. per week to maintain a level between 28 and 35 seconds. She has had no further emboli and leads a rather active life.

B. C., a female, fifty-three years of age, developed rheumatic fever at twenty-eight years of age, and had five recurrences thereafter. She developed auricular fibrillation approximately five years before admission. It has been paroxysmal, with great variations in the duration of attacks. Her first recognized embolus occurred in 1944. This was cerebral and she became unconscious and was in bed for approximately six weeks. She made a complete recovery. The second embolus occurred on May 30, 1946, producing a sudden blackout. This was also probably cerebral. In June, 1946, she had emboli to both legs. On July 7, 1946, she developed a sharp pain in the right hip and also one in the chest followed by bloody sputum which was probably a pulmonary embolus. On July 14, 1946, she developed one to the right leg. Anticoagulant therapy was not started at that time but was begun on September 24, 1946. She received dicumarol while in the hospital for one month, since which time she has been ambulatory. She requires approximately 400 to 500 mg. of dicumarol per week. On December 16th, she began to have excessive menstrual

flow which continued for approximately 10 days. Her prothrombin time ranged between 24 and 28 seconds so it seems unlikely that this was responsible for her excessive flow. The dicumarol was discontinued and vitamin K, two doses of 64 mg. each, was given. A gynecologist believed that the excessive flow was due to menopausal changes and a dilatation and curettage was performed, followed by irradiation. She began her dicumarol again, thereafter, and there have been no emboli following dicumarol.

Other examples could be cited to illustrate this type of case and the problems which may be encountered.* It should be pointed out that these patients characteristically may go for many months or even for several years without embolic episodes. Therefore, caution should be used in evaluating the effects of therapy in any specific case. On the other hand, one should note that several of these patients were in serious condition and were having very frequent and alarming embolic episodes at the time anticoagulant therapy was begun. Eleven of the thirteen patients who are receiving ambulatory dicumarol treatment, and who have been able to follow this therapy with satisfactory prothrombin tests, have now gone for a total of seventy-five months (or more than six years total time), without an embolus. Two patients who have been unable to remain on satisfactory ambulatory anticoagulant regimens have had embolic phenomena following a course of dicumarol for one month or more in the hospital. One of these, as above reported, died. The results, while at present inconclusive, appear sufficiently encouraging to warrant further study and consideration of anticoagulant therapy in the care of this most unfortunate syndrome, hitherto practically unamenable to treatment.

USE OF ANTICOAGULANTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

The use of heparin in the treatment of subacute bacterial endocarditis has been controversial. Katz and his co-workers⁵¹ attempted to modify the course of this disease with heparin. Kelson and White⁵² also reported on its use in connection with sulfonamides but the treatment of this disease with sulfonamides, with or without heparin, was abandoned because successes were rare; and the recovery rate deviated little from that resulting from spontaneous remission independent of the use of either chemotherapeutic or anticoagulant agents. MacNeal, Marty and Poindexter,⁶¹ Dawson et al.,⁶² and Loewe and his co-workers⁶³⁻⁶⁶ were among the first to use penicillin therapy successfully in the treatment of bacterial endocarditis. Loewe et al. combined this with heparin therapy on the basis of observations that fibrin and blood elements served as an impenetrable barrier to effective chemotherapy. The offending organisms lying deep in the vegetation were well protected from circulating anti-infective agents. They believed that to accomplish disappearance of vegetations the combined use of a suitable chemotherapeutic agent and an anticoagulant was required. In Loewe's laboratory heparin was employed in experimental animals to arrest the deposition of blood platelets and fibrin which served as a protective nidus and as a stimulus for bacterial growth. They reported that relatively fresh, artificially induced thrombi in the animal could be dissipated following the use of anticoagulants. They also made observations on human postmortem material which they believed indicated that heparin had a possible erosive effect on endocardial vegetations. This experience was applied to human patients, using the continuous intravenous infusion of heparin and the fractional intravenous in-

*The first preliminary report was presented before the Philadelphia College of Physicians in November, 1946.

jection method. Since these methods had marked technical and clinical disadvantages, Loewe utilized a retarding base—the Pitkin menstruum—composed of gelatin, dextrose, glacial acetic acid and water. Although a prolonged anticoagulation effect was obtained, the use of the original preparations was complicated by local pain, occasional severe local reactions and nausea in some individuals. Loewe and his group, in collaboration with others, have been striving to obtain or perfect a more satisfactory menstruum. As above mentioned, they claim to have reduced these adverse effects while maintaining therapeutic effectiveness.* Our patients still complain of pain after injections of the newer preparations. Using combined penicillin-heparin therapy Loewe et al. have reported a recovery rate of 83 per cent in 115 consecutive and unselected patients with subacute bacterial endocarditis. This is a remarkable recovery rate in a disease formerly considered practically incurable. The question has been repeatedly raised as to whether heparin *per se* actually plays a part in this recovery rate. Other workers⁶⁷ have reported recovery rates from penicillin alone ranging from 60 per cent to higher than 80 per cent. There has been a considerable difference in the amount of penicillin which the various groups have utilized in the treatment of their patients and Loewe has employed the largest doses recorded. As far as the present author knows, there has been no definite correlation made as yet between the dosage used and the actual statistics reported in the various series. This would be useful. It might shed some light on the importance, or lack of importance, of heparin as a therapeutic agent. It was noted early in the use of penicillin that thrombophlebitis was a rather troublesome complication and Loewe pointed out that thrombophlebitis seldom

occurs in his heparinized patients, which would be one point in favor of using it. On the other hand, hemorrhagic manifestations and even death have occurred from the use of both heparin and dicumarol in the treatment of subacute bacterial endocarditis. The cause for these hemorrhagic manifestations in various areas of the body in cases of subacute bacterial endocarditis is not clear. One possibility appears to be that the effect of the disease is more widespread throughout the endothelial system than has hitherto been recognized. The work of Moldavsky, Hasselbrock and Cateno,³ and of Macht⁶ demonstrating the marked increase in the tendency toward thrombosis produced by the administration of penicillin should reopen this subject. Macht⁷ found that amorphous penicillin of every brand examined produced a marked acceleration of clotting time, whether injected intravenously or intramuscularly, or even when administered by a stomach tube mixed with aluminum hydroxide gel. The crystalline salts of the various types of penicillin were studied. They were found to affect the thromboplastic properties in the following order: The most potent was penicillin X (hydroxybenzyl penicillin), next came K (heptyl penicillin), G (benzyl penicillin) and F (pentyl penicillin). It was found, furthermore, that a small dose of penicillin X added to penicillin G produced a synergistic effect and hastened coagulation more than a dose of penicillin G alone. Since much larger doses of penicillin are now being administered in some cases of subacute bacterial endocarditis, the question of the use of anticoagulants to counteract the coagulant effect of massive doses of penicillin should be studied further. It is obviously undesirable to produce an increase in the thrombosing tendency when the patient is bedridden and a vegetation is forming within the heart. On the other hand, it is equally important to avoid facilitating hemorrhage.

* Personal communication from Dr. Leo Loewe.

At the present writing we must conclude that the evidence that anticoagulants favorably affect the results of penicillin therapy in subacute bacterial endocarditis is inconclusive. There is evidence that their use may increase the risk of hemorrhage. On the other hand, further study to determine their power to control the thrombosing tendency of the large doses of penicillin now used is justified at this time.

SUMMARY AND CONCLUSIONS

Thromboembolic phenomena occurring in all parts of the vascular tree, particularly in the heart, lungs, brain and peripheral vessels, produce the terminal episode in the lives of more persons over fifty than any other cause. A large proportion of these patients survive their first episode of thrombosis or embolism but die later of recurrences or of complications.

Treatment of heart disease in the past, while helpful, has in many ways tended to encourage further thrombosis, the very complication frequently most important to avert. The use of the anticoagulants heparin and dicumarol constitutes a logical procedure to combat this tendency to thrombosis.

The results of anticoagulant therapy in the treatment of thrombophlebitis of the peripheral veins, together with the secondary complications of this syndrome, are summarized. These reports are drawn from the experiences of the Mayo Clinic, the Swedish hospitals, and our own experiences in both military and civilian hospitals. They appear to demonstrate conclusively that this form of therapy is the most satisfactory used to date.

The evidence in favor of the value of anticoagulant therapy in the treatment of coronary thrombosis with myocardial infarction, especially in the presence of thromboembolic complications, appears definitely encouraging. Case reports are presented exemplifying this problem. Final evaluation

must await the results of large, carefully controlled studies such as that now being carried on in fifteen participating hospitals under the auspices of the American Heart Association and the U. S. Public Health Service.

The value of anticoagulant therapy in the treatment of rheumatic heart disease with auricular fibrillation and multiple emboli is under investigation. Detailed case reports of some of the first patients studied in this series are presented. The results warrant further study of this problem.

The evidence for the specific value of the addition of anticoagulant therapy to penicillin in the treatment of subacute bacterial endocarditis is inconclusive at this time. The increased tendency to thrombosis produced by massive doses of penicillin injects a factor which may reopen this subject for further study.

The efforts summarized in this paper represent a fresh point of view toward and a new method of attack upon some of the most difficult and heretofore insoluble problems of heart disease. The results, while at present preliminary, have been encouraging beyond expectations and justify more intensive exploration by this approach.

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Present Status of the Problem of Thromboembolism*

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DURING the past six months the Seminars on Thromboembolism have reviewed the concepts of this disease and have presented the results of the various schools of therapy. The increasing importance of the problem and the interest of the medical profession in attacking it has been reflected in the high caliber of the work reported from so many widely separated medical centers.

COAGULATION MECHANISMS

Ferguson,¹ in reviewing the basic mechanisms of coagulation, indicated the possible ways in which pathologic intravascular clotting may occur. It is the belief of many investigators that an as yet unidentified precipitating factor produces a state of accelerated coagulability of the blood which may then reveal itself clinically in one or more thrombotic phenomena. Present methods of estimating the state and speed of coagulation are admittedly gross and insensitive. However, a number of investigators have reported observations indicating alteration of blood coagulability under varying clinical conditions. (Table I.) These changes may in themselves predispose to abnormal clotting or they may indicate periods of actual hypercoagulability.

The most pressing need today in the thromboembolic problem is for a simple test for blood coagulation which is easily and quickly performed. By means of this test the individual with a propensity to pathologic intravascular clotting could be discovered in the prethrombotic period and aggressively and intelligently treated with

appropriate prophylactic measures, either medical or surgical.

During the past several years interest has been stirred by observations that certain drugs appear to exert a coagulation-accelerating or thromboplastic-like action. Digitalis was the first to be so incriminated. The original report¹⁹ was followed by studies by three other groups of investigators who noted that following and during digitalization the coagulation time,²⁰⁻²² the heparin tolerance²¹ and the dilute prothrombin time⁶ were reduced. Loewe¹⁶ goes so far as to say that because of this thromboplastic-like side effect digitalis should be avoided if possible during the period of heparinization. On the other hand, three reports^{23-24a} have been published showing completely negative findings with regard to acceleration of coagulation by digitalis preparations. Thus, the problem is not conclusively settled as to just what is the rôle of this side action of digitalis and of precisely what magnitude. It would seem logical to administer digitalis whenever it is indicated, particularly in congestive heart failure associated with cardiac infarction and the severe types of pulmonary embolism. Moreover, if anticoagulants are being employed in the management of a patient with a thrombotic problem, either heparin or dicumarol would theoretically be able to nullify any coagulant effect of the digitalis.

Equal interest has been aroused by preliminary reports^{25,26} that penicillin also appears to produce acceleration of coagulation. However, one investigator²⁷ has failed to demonstrate the presence of any thrombo-

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plastic-like activity exerted by penicillin in *in vitro* and *in vivo* tests. Some of the more highly purified commercially available penicillin preparations and the penicillin G fraction exhibit much less of this clot-accelerating activity. As with digitalis, this

EARLY AMBULATION

Early or accelerated ambulation of the post partum and postoperative patient, and even of medical and cardiac patients, has been considered to be a logical approach in attempting to reduce the incidence and

TABLE I

OBSERVATIONS INDICATING TENDENCY TO INCREASED COAGULABILITY OF THE BLOOD IN CERTAIN CLINICAL STATES

Test	Trend of Results	Clinical State Encountered	Investigator
Platelet count.....	Increased	Postoperative; post partum	Wright ²
Platelet count.....	Increased	Postoperative	Shapiro ⁴
Platelet adhesiveness.....	Increased	Postoperative; post partum	Wright ²
Blood coagulation time.....	Accelerated	Postoperative; post partum	Dawburn ³
12.5% dilute prothrombin time.....	Decreased	Thrombosis or pulmonary embolism	Shapiro ^{4,5}
Whole or dilute prothrombin time.....	Decreased	Acute coronary thrombosis	Peters et al. ⁶
Plasma clotting index.....	Increased	Thromboembolism	Bancroft ⁷
Intravenous heparin tolerance.....	Increased	Acute thrombosis	de Takats ⁸
Heparin retarded clotting time.....	Flattened curve	Bed rest; acute inflammations; post-operative	Waugh ⁹
Modified heparin retarded clotting time.....	Decreased	Acute coronary thrombosis	Ogura ¹⁰
Dilute prothrombin time.....	Decreased	Acute coronary thrombosis	Meyers ¹¹
Venous clotting time.....	Decreased	Venous blood from acute thrombophlebitic extremities	Shafiroff ¹²
Dilute prothrombin time.....	Decreased	Venous thrombosis; pulmonary embolism	Cotlove ¹³
Whole and dilute prothrombin time.....	Decreased	Post partum	Norris ¹⁴
Venous clotting time in lucite tubes.....	Decreased	Thrombophlebitis	Kadish ¹⁵
Platelet clustering.....	Increased	Thromboembolism	Loewe ¹⁶
Heparin dose necessary to produce usual prolongation of venous clotting time.....	Increased	Acute thrombosis	Loewe ¹⁶
Blood coagulation time.....	Decreased	Postoperative; post partum	Dawburn ³
Clot retraction time.....	Accelerated	Pulmonary embolism	Hirschboeck ¹⁷
Blood "fibrin".....	Increased	Postoperative	Walters ¹⁸

alleged liability of penicillin is not considered at present to be a contraindication to its use either in thromboembolic cases or in infections. After more experimental and clinical evaluation the actual rôle played by penicillin as a possible inciting agent in intravascular clotting may be more judiciously weighed. The evidence now is far from sufficient to warrant administering anticoagulants prophylactically when penicillin is given or to withhold penicillin, because of its possible thrombotic threat, from a patient in whom it is indicated.

Wright²⁸ has summarized the present status of aminophylline as a coagulant. The evidence to date fails to establish any coagulation-accelerating or hyperprothrombinemic activity of this drug.

mortality of thromboembolism. It was believed that venous stasis and the sluggish circulation of a person in bed would be altered advantageously by earlier mobilization, thus eliminating a factor considered to be of major importance in the production of thrombosis. Some reports of series managed by early ambulation have indicated a significant reduction in incidence and mortality both as regards peripheral thromboses and pulmonary embolism. Jorpes²⁹ accumulated statistics on early ambulation from the European clinics in which the occurrence of thrombosis was reduced up to one-half of the original figure. At the same time, he concluded that such measures do not provide full security against the occurrence of this complication. Canavaro³⁰ reported a re-

duction in incidence of thrombotic phenomena of over 50 per cent (from 2.4 to 1.0 per cent) in a series of 500 surgical patients ambulated in the early postoperative period. Leithauser,³¹ an enthusiastic advocate of accelerated ambulation, reported a series of over 2,000 patients under his observation in which no pulmonary emboli and only two instances of thrombophlebitis occurred.

On the other hand, Blodgett³² studied 238 cases of early postoperative ambulation at the Massachusetts General Hospital and failed to find any decrease in thrombotic complications, even noting a statistical increase in the incidence of phlebitis, pulmonary infarct and deaths due to pulmonary emboli. During the past two years it has appeared to the author that there are definitely more cases of thromboembolism occurring currently than ever before, whether due only to the increased alertness in diagnosis or also to an absolute increase in the occurrence of this disease is not clear. This impression prevails despite the emphasis currently placed upon the avoidance of unnecessary bed rest and the general adoption of programs of early ambulation. Powers³³ has analyzed his experience in a large group of patients under his direct supervision and failed to demonstrate any reduction in the occurrence of thromboembolic phenomena. The fatalities from pulmonary emboli were decreased by 50 per cent. However, Powers rightly points out that recently adopted definitive treatment (by vein ligation in his clinic) must claim at least part, possibly the major part, of the credit for the reduced mortality rate. At any rate, it is now even more apparent that although accelerated ambulation is physiologically sound and a step in the right direction, it is far from the panacea or complete prophylaxis of thrombosis that had been hoped not so long ago. Other and more specific prophylactic measures are worth while and necessary. Even more, a high index of suspicion of thrombosis must always be present in the clinician's mind in order to diagnose the process and institute specific treatment as early as possible. He should

not be lulled into a false sense of security because he sees to it that his patient is out of bed as soon as possible. The physician's obligation in avoiding thrombotic complications has not been met merely by ordering early ambulation.

VENOUS THROMBOEMBOLIC DISEASE

Prophylaxis. Inasmuch as avoidance of unnecessarily prolonged bed rest by accelerated ambulation has not eliminated thrombotic phenomena, it is only logical to attempt to single out those individuals who are in situations which clinical experience has shown to predispose to thromboembolism (e.g., postoperative, cardiac infarcts, etc.). Active specific prophylactic measures could then be carried out, either by the use of anticoagulants or by peripheral venous ligation.

Extensive clinical observations and critical analyses of many series of patients indicate that the following facts are pertinent to the detection of thrombosis-susceptible patients:

1. A history of previous thromboembolism predisposes to recurrence, particularly if that individual again becomes postoperative or post partum.
2. Disturbances of venous circulation, such as extensive varicosities, favor the development of thromboses.
3. Individuals with malignancy suffer more frequent and recurrent thromboses.
4. Extensive abdominal and pelvic surgical procedures, particularly those performed for malignancy (such as abdominoperineal resection for cancer of the rectosigmoid), are complicated by far more than the average number of thrombotic phenomena (about 35 per cent in our experience).
5. Fractures of the femur and amputations of lower extremities are followed by a remarkably high incidence of thromboembolism (as high as 10 per cent of fatal embolism in older patients).

6. More than 60 per cent of all postoperative venous thromboses and emboli occur in the age group over fifty years and more than 80 per cent in the age group over forty years.
7. Thromboembolism occurs at least twice as frequently in obese individuals as in those of normal weight.
8. Cardiac insufficiency, with its attendant disturbances of venous return, greatly increases the risk of thrombotic episodes.

Indications for prophylactic therapy, such as the aforementioned factors, are still being drafted and put to therapeutic test. Recent reports, particularly from the Mayo Clinic,³⁴ Allen and his group at the Massachusetts General Hospital,³⁵ Murray in Canada³⁶ and Crafoord in Sweden,³⁷ indicate a significant decrease in the incidence of and deaths due to thromboembolism following institution of active specific prophylactic measures (i.e., anticoagulants or vein ligation). The results obtained in the field of prophylaxis by both medical and surgical management are comparable and encouraging.

Diagnosis. The clinical diagnosis of venous thrombosis and pulmonary embolism was discussed by the Columbia and Cornell Conferences,^{38,39} by Loewe¹⁶ and was also well outlined by Homans in a previous publication.⁴⁰ Essential to the proper care of patients with thrombotic problems is an understanding of the mechanism of the development of deep venous thrombosis, particularly in the lower extremities.³⁸ The clinician should possess a mental picture of the two clinical extremes of venous thrombosis (phlebothrombosis and thrombophlebitis) and the manner in which a pulmonary embolus evolves from peripheral deep thromboses; he should also be alert for the earliest evidence of the presence of thromboembolic disease. Homans⁴¹ has differentiated instructively the two phases of pulmonary embolism, i.e., the embolic phase and the phase of infarct production. Patients in these phases differ symptomatically and present varying physi-

cal findings. X-ray evidence may be absent in the purely embolic phase. It is not amiss to re-emphasize that the occurrence of pleuritic pain in a postoperative, post partum or cardiac patient or the occurrence of hemoptysis, particularly in a cardiac patient, should immediately suggest the possibility of embolism. Under such circumstances the slightest clinical indication of deep venous thrombosis should be weighty evidence confirming the impression that pulmonary embolization has occurred. Bearing in mind that as many as 50 per cent of pulmonary emboli occur without clinically recognizable peripheral venous thrombosis at the time of embolism,^{39,42} the absence of clinical evidence of peripheral venous thrombosis should bear no weight whatsoever against a diagnosis of pulmonary embolism. If venous thrombosis is present, the diagnosis can be made that much more easily.

Rationale of Therapy. The major objectives of therapy in deep venous thrombosis and/or pulmonary embolism are: (1) The proper management of the original episode of acute pulmonary embolism so as to reduce, insofar as possible, the associated mortality rate; (2) the prevention of subsequent massive pulmonary emboli which may be fatal; (3) the proper handling of the thrombotic occlusion of the deep venous system so as to retain as near normal the state of venous competency in the post-thrombotic years and thus to avoid the troublesome "postphlebotic syndrome."

The advocates of surgery argue that complete interruption of the pathway which 90 per cent of emboli are believed to traverse is not accomplished by medical methods. Ligation is said to offer the patient a complete and permanent type of protection without the added risk of hemorrhage. The anticoagulant group agree that this contention, particularly in reference to bleeding, may well be borne out in certain situations (e. g., neurosurgical and prostatic surgery). On the other hand, the medical proponents believe that the thrombotic process or embolus is merely a local manifestation of a generalized thrombosing tendency. They

argue that if prophylaxis against subsequent fatal emboli can be obtained without the discomfort or risk of an additional operation, this is desirable. The medical approach is believed to be more physiologic and equally effective as borne out by clinical reports. Bleeding of significant degree occurs in not more than 1 to 2.5 per cent of cases^{34,42} and deaths are extremely rare with adequately controlled therapy.

Murray³⁶ has emphasized the usefulness of heparin administration in the patient with acute severe pulmonary embolism. He believes that propagation of thrombus material from the site of embolus lodgment may be avoided if anticoagulant administration is immediately started and the incidence of fatality due to the original acute episode thus reduced. De Takats⁴³ analyzed a group of patients who died from pulmonary embolus and concluded that 60 per cent live for a period of one hour to several days. If the cause of some of the delayed deaths from pulmonary embolism is the propagation of thrombus material in the pulmonary artery, a fertile field of endeavor is opened to the employment of anticoagulants. A recent report from the Massachusetts General Hospital⁴⁴ stated that thrombus formation proximal to the site of venous ligation was found in more than 50 per cent of a small group of medical pulmonary emboli cases who were treated by ligation and later examined at autopsy. These two preceding reports suggest that there is a rational basis for the employment of anticoagulants even as an adjunct to ligation. This subject was discussed in the Cornell Conference²⁹ and by Homans.⁴¹

In one analysis of cases³⁴ a fatal pulmonary embolus occurred in approximately 6 per cent of patients with deep venous thrombosis and in 18 per cent of those individuals who had already experienced one non-fatal pulmonary embolus. The primary objective of all therapy employed in venous thromboembolism is the reduction of this particular mortality rate to the lowest possible figure. This result is being achieved equally well by anticoagulants and by vein ligation

as attested by the statistics from both proponents.^{16,29,34,35,36,38,40,42} The Columbia Clinic²⁸ analyzed the available over-all experience of many groups with anticoagulant management. It was determined that subsequent fatal embolism occurred in 0.3 per cent of 2,327 cases of deep venous thrombosis and in 0.9 per cent of 887 cases of initially non-fatal pulmonary embolism.

The troublesome complaints of the phlebotic patient months and years following the acute episode of phlebitis are familiar to most practitioners and have been considered in detail by Homans,⁴⁵ Bauer⁴⁶ and Buxton.⁴⁷ Bauer⁴⁶ reported a small group of patients with deep venous thrombosis localized to the leg below the level of the popliteal vein who were treated with heparin and investigated both pre- and post-treatment by phlebography. He noted that the level of venous occlusion did not ascend further once therapy was started thus avoiding compromise of the important, strategically located popliteal vein. As brought out in the Columbia Clinic,³⁸ Bauer, after a three-year follow-up, further observed a very marked difference in the incidence of both subjective and objective postphlebotic difficulties between the anticoagulant-treated group and a comparable series of patients receiving no active therapy. Similar evaluation of surgically managed patients is not available and is awaited by all interested clinicians.

Loewe's¹⁶ observations on the dissolution of "sludge" thrombus material by heparin are important. This phenomenon may account for some of the remarkable improvement seen in extremities with acute venous thrombi shortly following initiation of anticoagulant treatment. It may also explain how a greater length of normal functioning vein is retained after the acute episode has subsided.

Surgical Therapy. Opponents of ligation have often stated their fears of troublesome edema and ulcers subsequent to ligation of such important venous channels. One earlier report⁴⁸ indicated that edema was present immediately following ligation in 80 per cent of common femoral and 45 per cent

of superficial femoral vein interruptions; edema was observed at a later follow-up period in approximately 40 per cent of both common and superficial femoral ligations. More recent reports make no mention of significant edema or ulceration after femoral vein ligation. The surgical proponents believe that ligation of the veins of the extremities does not produce difficulty in the circulatory dynamics and that complete block of the vessel up to the point of ligation does not necessarily occur. However, most reports on inferior vena caval ligation do remark on significant edema and even leg ulcerations³⁵ occurring shortly following operation.

Homans, who is generally considered to be the dean of the ligation school, has clearly stated⁴¹ what he considers at the present time to be the indications for and preferred levels of ligation. It is to be emphasized that he regards vena caval ligation *only as a last resort* to be employed when repeated embolism has continued to occur despite peripheral venous ligation and/or adequate anticoagulant administration. His statement that certain forms of peripheral venous thrombosis, in which pulmonary embolism has not occurred, may be adequately handled by medical management reflects a change in viewpoint by the surgical school. Ligation of the femoral veins under local anesthesia is classed as a "minor" operation; however, ligation of the common iliac and especially of the vena cava are by no stretch of the imagination "minor" operations and are to be considered as surgical procedures of a definitely major nature. Even femoral ligations may be technically difficult in the obese patient or in an individual who has an edematous, swollen thigh such as may occur in congestive heart failure or ileofemoral venous occlusion.

The morbidity and total duration of hospitalization following ligation is reported to average eight days.⁴⁸ This is definitely less than the hospital stay of anticoagulant-treated patients. With the possible exception of the Swedish school schedules,⁴⁹ the medical programs of therapy extend the treatment period to at least ten days and usually

average two weeks. Some clinicians extend the period of treatment as long as four weeks.^{16,39} This point may well merit consideration in analyzing results and the practicability of a method of therapy, particularly in a crowded municipal hospital.

Medical Therapy. Loewe¹⁶ has clearly and forcefully presented the case for heparin/Pitkin menstruum. He states that it has been possible to eliminate one of the greatest drawbacks of the menstruum, i.e., severe pain at the site of injection. Distressing discomfort accompanied almost each injection of the earlier product and forced discontinuance of treatment in many patients. Loewe states that 90 per cent of patients can now be satisfactorily and adequately managed (i.e., an adequate but safe elevation of venous clotting time achieved) with an average dose of 300 mg. every other day. This, if confirmed by other investigators, is of considerable practical aid to the physician who wishes to employ this form of treatment in general practice.

Murray³⁶ has supplemented his previous observations with another report on the successful use of the sodium salt of heparin by continuous intravenous infusion. A practical complaint concerning this mode of therapy is the difficulty of maintaining a continuous intravenous drip for a period of six to twelve days. Such prolonged venous therapy is difficult for the doctor as well as for the patient. This objection is not encountered with heparin/Pitkin menstruum or with a method of employing intermittent subcutaneous injection of the sodium salt of heparin. Dicumarol treatment also obviates this difficulty.

The cost of either heparin or heparin/Pitkin menstruum is many times that of dicumarol. This difference may be of practical importance to the physician who must treat a patient of modest means. It is equally pertinent to the administrative and professional hospital staff who are charged with deciding upon an effective yet economically reasonable method of handling thromboembolic disease. Although the ideal anticoagulant must be safe and reliable, it should also

be economically reasonable and readily available.

The Mayo Clinic report³⁴ on dicumarol is clearcut, fairly stated and instructive. Dicumarol is orally and therefore easily administered. Most groups employing dicumarol use supplementary heparin to obtain an immediate anticoagulant effect during the average forty-eight-hour lag period before adequate prolongation of the prothrombin time has been achieved by dicumarol. This program removes a main objection to the use of the slower acting dicumarol in acute thrombotic emergencies. Groups experienced with dicumarol believe that vitamin K and transfusion are more efficacious in combatting excessive prothrombin deficiency and hemorrhage than Loewe¹⁶ indicates. As indicated by Wright²⁸ and the Mayo Clinic reports,³⁴ the prothrombin test should be in the hands of an experienced technician or closely supervised by a physician thoroughly familiar with the technic. Some investigators^{50,51} believe that the dilute (12.5 per cent plasma) prothrombin time is more sensitive and a more accurate and safer guide to therapy than is the whole plasma determination. However, the dilute plasma test is more time consuming and errors of technic appear to be exaggerated. Most observers employing dicumarol^{28,34,42} believe that the dilute prothrombin test is not necessary for safe control of dicumarol administration and that whole plasma prothrombin determinations carried out according to the modified Quick method suffice. A laboratory or physician who wishes to employ prothrombin determination tests for control of dicumarol therapy should make certain of the constant potency of the thromboplastin employed. Significant variations in results are produced by changes in the quality of thromboplastin, variations of such magnitude as to render the tests unreliable for the control of dicumarol treatment. In order to broaden the applicability of prothrombin time tests so as to enable a physician with only an occasional patient receiving dicumarol to control the treatment, some commercial firms

are attempting to produce small kits complete with all materials necessary for the test. Wright²⁸ has described in detail a dependable technic for prothrombin determinations. Even so, if dicumarol treatment is to be made available for general medical practice, the greatest need is for a still simpler prothrombin test, preferably a bedside type more dependable than previous ones devised.⁵²

Many groups experienced with anticoagulants^{16,28,34,36,38,40,42,53} base their therapeutic dosage of heparin and dicumarol on the premise that continued elevation of venous clotting or prothrombin time is desirable. The Swedish anticoagulant group^{49,54} initially assumed that heparin exerted beneficial effects in thromboembolism in some manner not currently understood and that the gross and generally unsatisfactory clotting time determination did not accurately measure this antithrombosing property. They believe that continual elevation of the venous clotting time need not be mandatory. According to their premise, intermittent intravenous injections of heparin at intervals of six to twelve hours should suffice to bring about such alterations of the blood coagulating mechanism as to effect satisfactory end results in thrombotic disease. They treated a large group of patients by the method of intermittent intravenous injection. The results in this series^{29,49,54} compared favorably with any of the more customary medical or surgical methods. This is further evidence for the theory that anticoagulant drugs, at least the two principal ones, exert a common antithrombosing influence which is not accurately measured by present methods of clotting and prothrombin time tests. A recent preliminary report⁵⁵ by a group investigating this problem made observations on the electrical resistance of whole blood. Heparin was found to produce significant alterations in the electrical conductivity of whole blood, *in vivo* and *in vitro*, as measured by the resistance time. Some effect analogous to this may well be the common ground of action of anticoagulant drugs.

The dosage of heparin employed by the

Swedish group was much higher than customarily employed in this country and at the time of the reports occasioned some comment that doses of such magnitude could be given with impunity. Jorpes⁵⁴ inferred that the Swedish heparin was less potent than the American product. Wright²⁸ confirms these observations with specific data indicating that our heparin is approximately one-third more active than the Swedish. Anyone planning anticoagulant treatment on the Swedish principle should take cognizance of this significant difference in potency and adjust the dose accordingly. An even more practical modification of the Swedish plan is being tried at the Presbyterian Hospital.⁵⁶ The sodium salt of heparin is administered by intermittent subcutaneous injection at intervals designed to obtain elevation of the venous clotting time for only a portion of the period between injections. This method possesses the advantage that the drug can be administered without hospitalization of the patient thus eliminating the need for skilled venipunctures and close control of the venous clotting time. Such a departure from previous concepts of therapy can be judged properly only by the results in a large group of patients. These results must necessarily compare favorably with those obtained by continuous prolongation of venous clotting time.

Hemorrhage. Bleeding due to excessive anticoagulant effect must be carefully managed. The measures to be employed with hemorrhage secondary to prothrombin deficiency produced by dicumarol are generally effective.^{34,57} When heparin produces bleeding, routine management consists of discontinuance of the drug and blood transfusion. Blood transfusion is used either for blood replacement or to return the clotting time toward normal. Protamine sulfate^{58,59} in 1 per cent or 2 per cent solution administered intravenously returns the clotting time to normal within five minutes. The dose is usually 50 to 100 mg. of protamine sulfate. One mg. of heparin is believed to be neutralized by 1 to 2 mg. of the protamine solution. This preparation has been ad-

ministered to humans⁵⁹ without untoward effects. Observations of the effect of protamine on the rate of bleeding are not available in the literature. The immediacy of action of the antidote for heparin would appear to be a definite advantage of heparin over dicumarol although further and more extensive clinical experience is needed in the use of protamine.

Sympathetic Block. It is believed that paravertebral lumbar sympathetic block⁶⁰ plays a definite though small rôle in the therapy of venous thrombosis. In the first place, acute thrombophlebitis of the deep venous system is encountered relatively infrequently. In one carefully studied series of combined venous thrombosis and pulmonary embolism,⁴² acute inflammatory thrombophlebitis occurred in less than 10 per cent of the patients. Significant measurable arterial spasm secondary to acute phlebitis is rarely encountered. Thus, the situation indicating sympathetic block is not a common clinical problem. Furthermore, Loewe,¹⁶ Murray²⁶ and others⁴² have observed that anticoagulants allay vasospasm and the manifestations of the inflammatory phlebitis within a short time after starting therapy. However, it is generally agreed that severe pain in the extremities only partially relieved by the usual analgesics is definitely lessened following sympathetic nerve block. In addition, the persistent edema of an ileofemoral thrombosis frequently is rapidly reduced by this procedure. Most clinicians employ lumbar sympathetic block in the infrequent patient with acute inflammatory ileofemoral phlebitis. However, it is difficult to understand how paravertebral nerve block can prevent or reduce the incidence of pulmonary embolism. It would seem proper to consider such a measure as aimed only at symptomatic and objective improvement in the extremity. This would imply that whether or not nerve block is used one of the two specific methods for preventing pulmonary embolism is most assuredly indicated in acute thrombophlebitis of the deep veins. Emboli are encountered frequently enough

in patients initially presenting a picture of acute phlebitis to indicate specific therapy. Due to the technical difficulty of vein ligation below the level of the inferior vena cava in this type of case, anticoagulants appear to be the treatment of choice.

Local anesthesia also has a part in the management of the severe pleuritic pain subsequent to embolization. If the usual sedation measures are not successful, a procaine block of certain of the intercostal nerves frequently relieves the patient whose site of pleural irritation is located sufficiently lateral or anterior in the chest to allow proper local infiltration.

Phlebography has been referred to but twice in the Seminar, an indication of its present status. Loewe¹⁶ expressed the current feeling of most American authorities that the procedure possesses several marked limitations: (1) The individual variation in normal venous channels makes interpretation difficult; (2) clinical diagnosis is usually possible without recourse to a rather complicated diagnostic procedure; (3) phlebography is time-consuming, not inexpensive and not without discomfort to the patient; (4) it entails moving the patient in a period when he should ideally be kept at strict bed rest and (5) the method is feasible only in hospitals where special facilities and experience in interpretation are available. Bauer initially used phlebography to establish the diagnosis of deep venous thrombosis. Recent reports from Sweden, however, indicate that even there phlebography is being employed much less frequently.

HEART DISEASE

Cardiac Infarction. Wright²⁸ has compiled an excellent summary of the present status of anticoagulant therapy in heart disease. The currently published opinions and preliminary reports indicate that the introduction of anticoagulants appears to diminish thromboembolic complications which add to the morbidity and mortality of cardiac infarction. The reports of Ogura¹⁰ and Meyer,¹¹ indicating accelerated coagulability of the blood during the early days of a

cardiac infarction, provide additional basis for prophylactic measures to avoid thrombotic phenomena. The clinical experiences of physicians, who in years past have not infrequently observed complicating thrombotic and embolic episodes in the course of an otherwise uneventful cardiac infarction, are added confirmation of the logic of this new therapy.

It is believed that embolic phenomena from mural thrombi and peripheral venous thrombosis will certainly be reduced and further extension of the area of myocardial infarction prevented. Wright particularly has observed beneficial effects in stopping recurrent and progressive infarction. The conclusions of the extensive study of the American Heart Association will be eagerly awaited by all physicians. In the meantime, many are employing the anticoagulants in their own practice after having thoroughly considered the pros and cons of their use. In the light of the long period during which these drugs are administered (four to eight weeks), the inexpensiveness of dicumarol would appear to offer a real advantage over any form of heparin management. The advantages of immediate heparinization at the start of dicumarol therapy are debatable. However, it seems logical to obtain the anti-thrombosing effect as soon as possible. Fresh mural thrombi may be found at autopsy as early as twenty-four hours following onset of symptoms of infarction.⁶¹ Administration of this preliminary heparin may be satisfactorily accomplished with either heparin/Pitkin menstruum or by repeated intravenous or subcutaneous injections. The continuous intravenous drip is obviously best avoided in those situations when cardiac reserve may be substantially impaired.

A word of caution is indicated concerning the occasional case of dissecting aneurysm of the aorta which may be confused with cardiac infarction. If there is a reasonable suspicion of an aortic dissection, the start of anticoagulant therapy should await work-up and further observation. Patients with cardiac infarcts did manage to survive in great number in the days prior to the intro-

duction of anticoagulants and these drugs are not quite the most suitable treatment for an aorta in the process of dissection.

If a pulmonary embolus occurs in a patient convalescing from a cardiac infarction, not being treated with anticoagulants, that patient should be managed like any case of pulmonary embolus, either by the use of anticoagulants or by peripheral venous ligation. The tendency of physicians is to ascribe to a mural thrombus the source of any embolus occurring in an individual with recent cardiac infarction. Carlotti et al.⁴⁴ recently analyzed an autopsied series of a medical (predominantly cardiac [70 per cent]) group of patients with pulmonary embolism. The heart was found to be an infrequent source of the embolus (11 per cent), the source of which was usually (78 per cent) in the peripheral deep veins. It would thus seem that a cardiac patient in whom embolism to the lungs occurs should either have his peripheral veins ligated or receive anticoagulants even though no clinical evidence of deep venous thrombosis is present in the extremities. The early mortality in this series⁴⁴ of pulmonary emboli was 28 per cent in those treated by vein ligation compared to 50 per cent in those who received no specific treatment. This significant difference is proof that proper management reflects itself in a lower mortality rate. It would appear, however, that administration of anticoagulants is more convenient than ligation, particularly in those patients without evidence of peripheral venous occlusion.

Emboli from Intracardiac Thrombi. Wright's²⁸ results with anticoagulant treatment in patients with chronic fibrillation and embolic phenomena are encouraging and noteworthy. The accepted custom of sitting idly by while repeated emboli occur may now be discarded. Certainly an embolus occurring in a fibrillating cardiac, whether to the systemic or pulmonic circulation, is an indication for proper and profitable use of anticoagulants. Propagation of fresh thrombus material at the site of lodgment of the embolus will be prevented as

well as further thrombus formation in the auricle or ventricle. The prolonged dicumarol treatment suggested by Wright must necessarily be conducted with the usual individual on out-patient status. Wright's experience with ambulatory dicumarol therapy indicates that it is practical although the inability to control dosage closely makes it more dangerous than when carried out within a hospital. Ambulatory dicumarol administration has also been conducted successfully by Nichol,⁶² Peters⁶ and Putnam.⁶³ Against this experience must be countered the sobering statement from the Mayo group³⁴ that ambulatory dicumarol therapy is inadvisable unless controlled by prothrombin determinations done at frequent intervals. It would appear that a decision to institute ambulatory anticoagulant treatment should be based on a careful consideration by doctor and patient of the potential risks of each alternative, i.e., bleeding versus embolism to a vital area. Dicumarol obviously has manifold advantages over heparin for this type of prolonged ambulatory therapy.

Subacute Bacterial Endocarditis. Wright²⁸ expressed the opinion, which seems to be generally held with the possible exception of Loewe,⁶⁴ that anticoagulants are ineffective in subacute bacterial endocarditis except when there is embolic occlusion of a large artery. Recent reports⁶⁵⁻⁶⁹ from clinicians who have intensively studied this problem conclude that the crux of the efficacy of therapy in bacterial endocarditis lies in the principle of adequate dosage of antibiotics over sufficient periods of time. They believe that anticoagulants are not necessary adjuncts. The ability of penicillin to penetrate fibrin⁷⁰ may partially explain the difference between the effectiveness of treatment with antibiotics today and that of five years ago with the sulfonamides. The sulfonamides do not possess this fibrin-penetrating characteristic. It would appear that anticoagulant therapy does not contribute enough to the cure of the infection to warrant the added danger of sustained hemorrhage from ruptured mycotic aneurysms or from the gen-

eral vascular fragility in this disease. The expense of the drugs and the tests necessary for the proper and safe control of administration are minor but definite added considerations. The discomfort to the patient of additional venipuncture or hypodermic injection is not negligible.

MISCELLANEOUS PROBLEMS OF THROMBOSIS

Arterial Occlusion. The introduction of the aggressive use of heparin and dicumarol in the management of acute peripheral arterial occlusions constitutes an exceedingly important and relatively new addition to our therapeutic armamentarium for the handling of such emergencies. To those with considerable experience in managing such problems surgical intervention in the form of embolectomy or thrombectomy has been far from satisfactory, due partly to difficulties in the localization of the exact site of occlusion, to frequent reforming of a thrombus at the site of incision and to the intense arterial spasm not infrequently incited by operation. The Mayo Clinic^{34,71} is particularly encouraging in their recent reports on the conservative method using anticoagulants plus measures to alleviate reflex vascular spasm. The still all important element of time in relation to the delay between vascular occlusion and initiation of therapy is emphasized by the Mayo statistics.⁷¹ When treatment was initiated twenty-four hours or longer after the occurrence of the embolic occlusion, ischemic necrosis occurred in 90 per cent of the patients but in only 25 per cent when treatment was started earlier. In arterial thrombosis, ischemic necrosis occurred in 80 per cent of patients when treatment was started more than twenty-four hours after onset but in only 50 per cent when appropriate measures were initiated earlier. The precise situation in which surgical intervention is indicated is difficult to define. It is accepted that embolectomy may be the treatment of choice in certain situations. It is only fair to believe that the results of surgical thrombectomy will be definitely improved by employing concurrent anticoagulant treatment pre- and postoperative. However, at present

it is believed that a trial of medical treatment is proper for at least eight to twelve hours before performing surgical procedures. An immediate antithrombosing effect is obviously best accomplished by some form of the immediately-acting heparin. After the first one to three days either dicumarol or heparin will be found adequate for maintaining the altered state of blood coagulability. Reflex arterial spasm should be alleviated by papaverine and/or an appropriate form of regional anesthesia. A pharmacologic block of the sympathetic ganglia may be attempted by agents such as tetraethylammonium^{72,73} but further evaluation of these drugs in such acute situations is necessary before entire reliance is placed upon them.

Frostbite Gangrene. The problem of frostbite gangrene has been intensively studied by Lange and his associates.⁷⁴ They have observed that red cell "sludge" forms in the capillaries following exposure to severe degrees of cold. The ischemic necrosis secondary to frostbite presents the histopathologic picture of a thrombotic process due to red cell agglutinative thrombi in the small vessels. If animals or human volunteers were heparinized as late as forty-eight hours following exposure and the anticoagulant therapy continued for seven to nine days, ischemic necrosis and massive gangrene were prevented; within this time, tissue death consistently occurred in the control animals or humans. These observations and their therapeutic implications are obviously of significant practical import to physicians who encounter this civilian and military hazard. The introduction of this mode of therapy is the first logical and effective advance in the management of a hitherto very unsatisfactory therapeutic problem.

CONCLUSIONS

It is clear from the reports that have appeared in these Seminars on Thromboembolism that there are available at present two extremely effective methods of therapy for venous thromboembolic disease. The various forms of heparin and dicumarol

therapy should be considered complementary rather than alternative modes of treatment. Vein ligation is an alternative to medical therapy whenever it appears unfeasible to carry out an adequate program of anticoagulant management. In like manner, when surgical therapy is the favored treatment, anticoagulants should be considered as the alternative method and should be instituted whenever vein ligation is not practical. Either medical therapy with anticoagulants or surgical vein ligation should be carried out as an emergency procedure in every case of deep venous thromboembolism.

The ultimate decision as to the most efficacious management of thromboembolic problems must be deferred until critical follow-up studies on sufficiently large groups of patients become available.

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Thromboembolism

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, N. Y. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. YALE KNEELAND, JR.: The subject of today's clinic is indicated by that new double-barreled word "thromboembolism" and like the word the subject itself in a sense is new. A standard textbook of surgery published in 1936, only eleven years ago, characteristically dismissed the subject in two or three sentences. The statement was made that pulmonary embolism sometimes occurred following surgical operations and that it was a dangerous complication, not infrequently fatal. Thrombophlebitis was stated to be a disease of the lower extremities characterized by pain and swelling and treated by bed rest with elevation of the limb. One had the impression in those days, only a decade ago, that thromboembolism in its various manifestations was an act of God about which very little could be done and it was more pleasant not to think too much about it. That situation has now changed. In introducing the newer aspects of the subject, I should like to call first upon Dr. Cross to discuss briefly the pathogenesis, mechanisms and clinical symptoms and signs of thromboembolism.

DR. RICHARD J. CROSS: Not much is known about the underlying pathology of thromboembolism. Apparently, most cases are associated with an abnormality in the clotting mechanism. Certain modifications of our routine tests reveal that the blood of these patients tends to clot a little more readily than that of patients with normal blood; however, this finding has not been correlated with what is known about the clotting mechanism and we cannot state just what the abnormality is.

Certain predisposing factors are known. Of major importance is venous stasis. While venous thromboses do occur in otherwise healthy individuals who have been enjoying full activity, the majority of cases develop in people who have been confined to bed, particularly in elderly or cachectic individuals with poor muscle tone. Tissue damage is apparently another precipitating factor in many cases. It may be that the damaged tissue releases a thromboplastic substance which gives rise to the above mentioned abnormality of the clotting mechanism.

It has recently been shown that the site of origin of venous thromboses is usually in the muscular branches of the deep veins of the calf or in the plantar veins of the foot. Involvement of other veins occurs rarely.

There are some authorities who believe that the foregoing remarks should be limited to those patients with venous thrombosis in whom there is very little inflammatory response. They refer to these as "phlebotrombosis," while the others with a widespread inflammatory reaction are referred to as "acute thrombophlebitis" and are believed to be due primarily to an inflammation of the vein wall of unknown etiology with clotting a secondary phenomenon. However, in our experience the majority of cases fall between these two extremes and the picture may shift from one to the other as I shall show you shortly.

Let us now consider the different phases in the formation of a thrombus in a muscular branch of the deep venous system of the calf, attempting to correlate the pathology with the symptoms, signs and laboratory findings.

(Table I.) The thrombus probably starts as a layer of platelets on which a clot forms, the end of the clot being carried up proximally by the flow of the blood. At this stage there is no obstruction of any vein. There is no inflammatory response and there are no symptoms, signs or laboratory findings.

TABLE I

VENOUS THROMBOSIS; SYMPTOMS, SIGNS AND LABORATORY FINDINGS AT DIFFERENT STAGES

- A. None
- B. Calf fullness
 - Tenderness over veins
 - Positive venogram
- C. "Dead" feeling
 - Swelling
 - Positive Homans' sign
 - Fever
 - Leukocytosis
 - Elevated erythrocyte sedimentation rate
- D. Severe pain
 - Extreme tenderness
 - Marked swelling
 - Pallor
 - Absent pulses
- E. Ankle edema
 - Palpable vein

The clot grows until it occludes the vein and we might then anticipate that there would be edema in the muscle which is drained by that vein. This is apparent clinically by a feeling of fullness in the calf muscles so that the affected calf feels more firm and less flabby than the other. We have found this sign to be the most reliable evidence of an early thrombosis. In addition, there is often a slight inflammatory response in the vein wall where the clot first formed. This, as might be anticipated, will give rise to a localized area of tenderness in the calf noted in almost all of our patients although more difficult to interpret since it is not an objective finding. The only other procedure which might help us to make the diagnosis at this early stage is a venogram. This is performed by the injection of radio-opaque material into an ankle vein, followed immediately by x-rays of the leg. These films are studied to see if the deep venous system fills completely. This procedure has been used quite widely in Sweden but most of the workers in this country who have tried it have not found it satisfactory because they cannot differentiate thrombosis from failure

to fill because of venous spasm or other factors.

The thrombus also grows proximally, forming a "red tail" which waves freely in the blood stream extending up into the larger venous channels. This causes neither disturbance of the circulation nor inflammatory response and we usually remain unaware of its presence unless a piece breaks loose and forms a pulmonary embolus.

Later, the lower part of this "red tail" becomes adherent to the walls of the larger veins, causing a more widespread and intense inflammatory reaction. The patient may have some pain but more commonly at this stage he complains of a feeling of discomfort in the calf, a 'heavy' or 'dead' feeling. There is now obstruction of some of the main veins and because of this and of the inflammatory response there will be some swelling of the calf as a whole as evidenced on inspection or, more precisely, by measurement. In addition, the inflammatory response will result in a positive Homans' dorsiflexion sign: on passive dorsiflexion of the foot there is pain in the calf. If the inflammatory response is intense enough, there will obviously be fever, leukocytosis and an elevated sedimentation rate. These have been stressed as diagnostic aids but we have not found them of great value. They are roughly correlated with the amount of inflammation present and we believe that the signs I mentioned earlier are more valuable evidence thereof.

As the waving "red tail" grows proximally, its area of attachment to the vein wall may also extend up the leg causing intense inflammation in the popliteal, femoral and iliac veins. At this stage there is often severe pain and extreme tenderness with redness and marked swelling, due not so much to venous obstruction as to the intense inflammation. In a few of these cases there is a reflex vasospasm which results in pale, cold extremities with absent pulses giving the typical picture of arterial occlusion. This is the syndrome which is described by Ochsner and others as the "acute thrombophlebitis" to which I re-

ferred earlier but we have seen it develop in the general fashion which I have described. At this stage there is far less danger of pulmonary embolism because the inflammatory response fixes the clot to the vein wall and it is a common clinical observation that "acute thrombophlebitis" is far less apt to be followed by pulmonary infarction than is benign "phlebothrombosis" with few or no signs.

The final stage occurs when the thrombus has become organized and when all exposed surfaces have become covered with a layer of endothelium. At this time embolism is impossible and there is no reason to anticipate fresh thrombus formation. There will often be a certain amount of ankle edema on a mechanical basis. This will usually clear as collateral circulation takes over in the course of the next few months. Depending upon how superficial the vein and how good the muscle tone, one may or may not be able to feel the thrombosed vein as a hard cord.

It is important to realize that although I have described this process in separate stages, it actually develops continuously. The distal part may be completely organized while the free "tail" is still growing proximally. Since abnormal findings depend upon the amount of venous obstruction and inflammation present, they give us no indication of how much free clot may have formed and it is all too common for fatal emboli to break loose from leg veins without giving rise to any of the symptoms, signs and laboratory findings I have described. There are no precise data available as to the time factors involved and these are probably quite variable but there is some evidence that any given segment of a thrombus becomes fixed to the vein wall within five days of its formation; and if growth of the thrombus can be prevented, that which is present will probably be endothelialized completely within ten to twelve days.

Next I should like to discuss the signs and symptoms of pulmonary embolism. Obviously, they will depend upon the size of the embolus. A small embolus may cause transient damage only, without infarction,

while a massive one may completely occlude the pulmonary artery. In general, the small emboli go out to the periphery of the lung and cause an inflammation of the pleura with resulting pleuritic pain, a symptom which we found in almost all of our patients. A larger embolus will tend to give a more intense pleuritic response, reflex changes and, therefore, dyspnea. As the result of the damage to vessel walls, there will be exudation of fluid and crepitant râles will be heard. That is the most reliable physical sign of pulmonary embolism which we have found. If you listen persistently and repeatedly, you will often succeed in putting your stethoscope over the area of pleura involved and hear a friction rub. In the case of left lower lobe infarcts this rub may have a pericardial element. At a later stage there will be consolidation with the physical signs thereof and characteristic x-ray findings. However, if the infarct is not large, the chest x-ray is often entirely normal particularly in the early stages. If any abnormalities are found, they usually consist of indefinite hazy shadows; the classical wedge-shaped shadow which is described in the literature has been rarely encountered by us. Pleural effusion occasionally occurs as a result of this pleurisy, a fact which should be borne in mind in considering the differential diagnosis of pleural effusion. If there is a sufficient area of the lung involved, there will, of course, be fever, leukocytosis and an elevated sedimentation rate. (Table II.)

With large infarcts the picture is often quite different. The large embolus does not approach the periphery of the lung but is stopped near the hilum. We have seen several patients who complained of a non-pleuritic, deep, visceral type of pain, presumably mediated through the autonomic nervous system, which was followed a day or two later by pleuritic pain; this we interpret to mean that the infarcted area has spread out to the periphery. Such patients often appear critically ill with marked cyanosis and severe dyspnea. Cough, however, is relatively rare and the hemoptysis described in most textbooks is, in our experience, even

rarer. The obstruction to one of the main branches of the pulmonary artery will obviously cause hypertension in the lesser circuit. It may be noted that the pulmonic second sound is louder than it was before. Occasionally, there are electrocardiographic

TABLE II

PULMONARY EMBOLISM; SYMPTOMS, SIGNS AND LABORATORY FINDINGS WITH EMBOLI OF DIFFERENT SIZE

- A. Very Small Emboli
 - None
- B. Small Emboli
 - Pleuritic pain
- C. Medium Emboli
 - Dyspnea
 - Râles
 - Friction rub
 - Signs of consolidation
 - X-ray shadow
 - Pleural effusion
 - Fever
 - Leukocytosis
 - Elevated erythrocyte sedimentation rate
- D. Large Emboli
 - Non-pleuritic pain
 - Severe dyspnea
 - Cyanosis
 - Cough
 - Hemoptysis
 - Loud pulmonic second sound
 - Electrocardiographic changes
 - Acute right heart failure
 - Abdominal signs
 - Jaundice
- E. Massive Emboli
 - Death

changes, both because of the changes in pressure and also on the basis of autonomic reflexes. The pulmonary hypertension may be severe enough to cause acute heart failure. Should the diaphragmatic pleura be involved, there may be abdominal signs with spasm and rigidity in the upper abdomen. Jaundice has been reported to be caused by pulmonary infarction but so far we have not observed it. Finally, of course, there may be massive emboli with death within a few minutes.

It must be obvious to all of you that pulmonary embolism may cause a clinical picture very similar to that of pneumonia, myocardial infarction and many other conditions. Differential diagnosis is essentially an individual problem and cannot be solved by any general rules. In my opinion, the one unforgivable sin is also the most common

one, namely, failure to keep the possibility of pulmonary embolism constantly in mind, especially when faced with some atypical pulmonary condition.

STUDENT: How often are fever and tachycardia the first evidence of thromboembolism?

DR. CROSS: In our experience, it is unusual to find fever caused by venous thrombosis in the absence of any local evidence of inflammation, even though that evidence may first be discovered in the course of a complete examination of a patient with unexplained fever. However, it is entirely possible to have a small pulmonary infarct deep in the lung which will give no evidence of its presence except by fever, tachycardia and tachypnea.

DR. KNEELAND: With this admirable clinical background for the conditions under discussion, we would now like to present to you two cases. The first, I shall present in the form of a brief abstract of the clinical record of a patient admitted here in October, 1944, just two and one-half years ago. This patient was a motorcycle policeman thirty-four years of age who entered with the chief complaint of chest pain, pleuritic in character, of two and one-half weeks' duration. It was noted on taking the man's history that he described an injury to his knee sustained while roller skating about eight weeks before admission. This had been sufficiently severe to incapacitate him with pain and swelling of the knee for a few weeks. Then he went back to duty, presumably to his former occupation of riding a motorcycle, the mechanics of which have an obvious bearing on what is to follow.

Two and one-half weeks before admission, he had had a sudden pain in the right chest, pleuritic in character. His local physician put him to bed and gave him a few doses of sulfadiazine on which he improved. After a week he was well enough to want to go back to work but his physician made him stay at home. Four days before admission here, he had an x-ray picture taken which showed fluid in the right chest; then on the following day he had a new bout of

pleuritic pain, again in the right lower chest and for the first time he noticed blood in his sputum. He had had no chills, no fever, very little cough and little shortness of breath.

On admission here he was found to be slightly cyanotic and slightly short of breath. His heart rate was 110. He had signs of a small amount of fluid in both pleural cavities and this was substantiated by x-ray examination. His white count was 10,000 with 72 per cent polymorphonuclears. In addition to the small effusion in both pleural cavities, there was a shadow in the right lower lung field. He was treated for pneumonia with full doses of sulfadiazine. Seven days later, after an uneventful clinical course, the patch in the lung had disappeared almost completely and further absorption of the fluid had taken place. On the tenth hospital day, when apparently fully recovered, he suddenly sat up in bed, gasped, turned very pale and then cyanotic and died of respiratory failure in twenty minutes. At autopsy extensive phlebothrombosis of the lower extremity was found together with old and fresh massive pulmonary infarction.

This case is presented to serve as a basis for comparison with the next case which Dr. Pons will present.

DR. EDUARDO R. PONS: Mr. D. B. is a fifty year old post office clerk who was born in the British West Indies. His past history is irrelevant, except for the fact that he has had varicose veins for many years and that seven years ago he had a superficial and deep thrombophlebitis of his right leg with subsequent mild residual edema.

A month ago he was admitted to the urologic service with symptoms of chronic urinary obstruction. A work-up revealed a median bar hypertrophy. Three weeks ago he had a transurethral prostatectomy from which he convalesced uneventfully. Early ambulation was carried out. On the fifth postoperative day, he noted a mild pain in his right lower leg and a sense of fullness in the right calf. He was nevertheless sent home on the sixth postoperative day and

returned to the regular follow-up clinic in urology a week later. At the time he had no urinary complaints but did complain of some pain in his right lower leg. He was then referred to the varicose vein clinic at which time an induration and tenderness over the right saphenous vein in its course over the lower leg was found. His pain had diminished in the week since discharge so he was considered to have a subsiding thrombophlebitis of a superficial vein and he was sent home to bed and told to wear an Ace bandage. The next day he suddenly experienced a sharp pleuritic pain in his right lower chest, without cough, without fever and without any symptoms of an upper respiratory infection. The pain persisted for three days after which he began to have fever with occasional spikes to 103°F. At the onset of fever, he was seen by his private physician who gave him penicillin, 300,000 units intramuscularly, every day for three days without any improvement of symptoms. In view of this lack of response, he was referred to the Presbyterian Hospital as a case of penicillin-resistant pneumonia. On admission one week ago, he appeared acutely ill and was mildly dyspneic. His temperature was 100.4°F. There were signs of extensive consolidation over the right lower lobe and right middle lobe, with dullness, egophony and classical tubular breathing. There were also a few râles at the left base. Chest x-ray confirmed the clinical impression of marked consolidation in the lower right lung and also showed some increased density in the left base.

On the ward the previous findings in the lungs were confirmed. In addition, he was found to have superficial tenderness and induration over the course of the internal saphenous vein on the right and also a sense of fullness in the right calf.

A review of the sequence of events, beginning with his postoperative leg pain and leading up to the presenting picture, justified a diagnosis of pulmonary infarction secondary to embolization from superficial and/or deep thrombophlebitis in the right lower leg. He was, therefore, started on

anticoagulants and penicillin was given prophylactically for secondary pulmonary infection of the infarcted area. His course in the hospital has been uneventful. During the past four days he has been asymptomatic and afebrile. The physical signs have changed slightly in that he now has minimal signs of fluid at the right base. The sputum, blood, and nose and throat swabbings have all been studied bacteriologically and have been found to be negative.

DR. KNEELAND: I should like to call your attention to the marked general similarity between these two cases. In each there was a disturbance of the lower extremity. In Case D. B. there was a fairly good clinical picture of thrombophlebitis and in the first case at least an injury. In each instance there was a long latent period. In each case there was a sudden development of pleuritic pain. The symptoms as described are almost superimposable. In each instance the patient was treated at home for pneumonia by his physician; in each instance he was sent to the hospital because of failure to respond to treatment and in each instance there was fluid in both pleural cavities and consolidation in the right lung as well. In the first instance, unhappily, the true diagnosis was not suspected; the patient was allowed to continue on routine treatment for a hypothetical infection of the respiratory tract and after a period of ten days in the hospital a final, massive, terminal embolization took place. The second patient, however, although admitted for pneumonia, was immediately recognized as a probable case of pulmonary embolism and the moment he arrived on the ward appropriate therapy was instituted. His course has been uneventful and he made a complete recovery.

The second case has been treated according to the methods employed by the group studying thromboembolism in this hospital. Dr. Cosgriff will now discuss these methods for treatment of thromboembolism by anticoagulants.

DR. STUART W. COSGRIFF: Thromboembolism posed a difficult problem in the days of conservative or expectant observation

therapy. If the patient was kept active and walking around there was a real danger of "fracturing" the thrombus which was present in the vein, thus producing a pulmonary embolus; on the other hand, if he were put to bed and kept quiet, there was an equally real possibility of adding to the propagation of the thrombus in the legs and thus building up more potential pulmonary emboli. Anticoagulant therapy has attempted to overcome this dilemma.

One of the first questions to be asked when considering anticoagulant therapy is: What is the basis for and what are the therapeutic objectives of anticoagulant therapy in thromboembolism? The aim of anticoagulant therapy is to modify the general blood coagulation mechanism of the body so that further propagation of the thrombus in the affected vein is halted and opportunity thus given for the natural inflammatory mechanism to fix the thrombus firmly to the vein wall. It has been demonstrated experimentally that between the second and fifth day a bland thrombus in an intact vein will become quite firmly attached so as to preclude embolization; that is the theoretical basis for our therapy. If pulmonary embolization has occurred, treatment aims also to prevent further propagation of the thrombus at the site of lodgment of the embolus in the lungs and more extensive lung tissue infarction.

There are several schools of anticoagulant therapy. One group advocating heparin aims at a continuous elevation of the venous clotting time. This is accomplished either by a continuous drip of heparin over a number of days or by repeated subcutaneous or intravenous injections of heparin at intervals, usually of three or four hours. The second heparin group is the Swedish school. They consider that heparin exerts some effect which we do not measure with the venous clotting time and that intravenous injections of heparin during a twenty-four-hour period produce an adequate anticoagulant effect even though the clotting time undoubtedly is not prolonged during this entire period. Another group employs

heparin in Pitkin's menstruum (a combination of glycerin, acetic acid and dextrose) which gradually releases heparin into the circulation over a period of hours. Each injection is usually intended to prolong the clotting time adequately for approximately forty-eight hours.

Dicumarol is frequently used as an anticoagulant. When employed alone, there is a lag period of approximately thirty-six to forty-eight hours before an effective prolongation of the prothrombin time is observed. Therefore, the usual therapy is to employ both heparin and dicumarol. The main drug is dicumarol, heparin being used during the first thirty-six to forty-eight hours for its immediate anticoagulant effect.

As regards the anticoagulant mechanism of heparin, it acts as an antithrombin, as an antithromboplastin, probably also as an antiprothrombin and finally it decreases the platelet agglutinability in the blood. Dicumarol also acts first and foremost as an antiprothrombin. Recent work indicates that it also exerts an antithromboplastin effect and that it decreases platelet agglutinability. Probably these two anticoagulant drugs exert further effects in a manner which we do not understand and do not measure by our present methods. For instance, dicumarol produces an effective anticoagulant response, as measured clinically and by the prothrombin time, although there is only an inconstant and irregular prolongation of venous clotting time. In like manner, heparin produces an adequate elevation of venous clotting time without necessarily prolonging prothrombin time.

The aim of anticoagulant therapy is the energetic treatment of the thrombosis which is already present and the embolism which may have already occurred; secondly, and more particularly, the prevention of further thrombotic and embolic episodes. We must be alert to diagnose and treat the small and relatively asymptomatic thromboses and infarcts as well as the extensive ones, to recognize cases early and to prevent the repetition of embolic phenomena which so often cause

death in pulmonary embolism. Of course, many of these patients with small pulmonary emboli recovered in the old days without any treatment but there were a substantial number who did not get better, who had repeated embolic phenomena culminating in a final fatal pulmonary embolus. Repeated embolization ending fatally is precisely what we are out to avoid with anticoagulant therapy.

DOCTOR: What are the expected complications and end results of venous thrombosis and of pulmonary embolus not immediately fatal?

DR. COSGRIFF: We have gathered some statistics from the American and European literature. It should be emphasized that the statistics for complications and mortality under conservative therapy are not directly comparable to the statistics for results of anticoagulant therapy. We are diagnosing venous thrombosis, particularly phlebotrombosis, and also pulmonary emboli much more frequently than we did five years ago. A number of these mild cases doubtless would do well under any therapy; however, it is my feeling that there may be an actual as well as an apparent increase in thrombotic disease during recent years.

Reports from American and European sources (Table III) comprising over 4500 cases of venous thrombosis indicate that approximately 21 per cent had subsequent thrombosis, 29 per cent had subsequent pulmonary embolus and 14 per cent had a subsequent fatal embolus. In the American group, considered separately, 900 cases under conservative treatment showed 12 per cent having subsequent thromboses, 19 per cent subsequent pulmonary emboli and 6 per cent subsequent fatal emboli.

We have studied thirteen reports (Table III) of the treatment of venous thrombosis with heparin and/or dicumarol. Of the total number of approximately 2200 cases under anticoagulant therapy, 1.1 per cent had a subsequent thrombosis, 1.2 per cent had a subsequent pulmonary embolus and 0.3 per cent had a subsequent fatal embolus.

Since we started our study at the Presbyterian Hospital (Table III), sixty cases of venous thrombosis have been treated. Subsequent thromboses have occurred in 3 per cent of those cases, pulmonary emboli in 1.7 per cent but no fatal emboli have occurred since treatment has been inaugurated.

mately 18 per cent of those cases. The Mayo Clinic reported 670 cases in greater detail showing that further thromboses occurred in 14 per cent, a subsequent pulmonary embolus in approximately one-third of the cases and a subsequent fatal pulmonary embolus in 18 per cent; that is, roughly one of

TABLE III
VENOUS THROMBOSES

	Number of Cases	Percentage of Cases Developing		
		Subsequent Thromboses	Subsequent Pulmonary Emboli	Subsequent Fatal Pulmonary Emboli
Conservative Therapy				
Total cases.....	4580	21	29	14
American cases.....	897	12	19	6
Anticoagulant Therapy				
Total cases.....	2267	1.1	1.2	0.3
Presbyterian Hospital cases....	60	3	1.7	0

TABLE IV
NON-FATAL PULMONARY EMBOLI

	Number of Cases	Percentage of Cases Developing		
		Subsequent Thromboses	Subsequent Pulmonary Emboli	Subsequent Fatal Pulmonary Emboli
Conservative Therapy				
Total cases.....	822	18.5
Mayo Clinic cases.....	678	14	30	18
Anticoagulant Therapy				
Total cases.....	817	1.1	1.1	0.9
Presbyterian Hospital cases....	80	2.5	3.8	1.3*

* One patient who died of massive fatal embolus ten minutes after the start of treatment.

I would like to draw your attention to the marked difference between the figures for mortality as given in Table III for the two different methods of treatment, conservative and anticoagulant. There has been a significant decline in the incidence of fatal pulmonary emboli since the inauguration of anticoagulant therapy.

As regards individuals who have experienced one or more non-fatal pulmonary emboli (Table IV) under conservative therapy, a fatal embolus occurred in approxi-

five people who had one pulmonary embolus which was non-fatal died of a subsequently fatal pulmonary embolus.

There are reports available on the use of anticoagulants in a total of 817 cases. Subsequent venous thrombosis occurred in 1.1 per cent, and subsequent non-fatal emboli in 1.1 per cent, subsequent fatal pulmonary emboli occurred in 0.9 per cent. At the Presbyterian Hospital we have employed anticoagulant therapy in eighty cases of pulmonary emboli with subsequent venous

thrombosis noted in 2.5 per cent and a subsequent pulmonary embolus in 3.8 per cent of the cases. One fatal pulmonary embolus occurred after the start of treatment, an incidence of 1.3 per cent.

There is a group of individuals in whom the possibility of thromboembolic phenomena appearing is much greater than in normal persons, namely, those with a previous history of thromboembolism, those with extensive varicosities, in cardiac disease, in some cases of carcinoma and after some abdominal operations. It is believed that the prophylactic use of anticoagulants is sound procedure when such individuals are postoperative or are subjected to enforced bed rest for some time because of fractures or medical conditions such as cardiac failure or infarction. In those subjects with a previous thromboembolic history, the risk of fatal embolism was determined by the Mayo group to be approximately 10 per cent. They have reported sixty-one such cases treated prophylactically without embolic phenomena and we have employed such measures in fifteen cases with similarly satisfactory results.

The Swedish investigators, in particular Bauer, have studied comparable groups treated under the previous "expectant observation" regimen and under heparin management. The clinical diagnosis in these patients was confirmed by venography with particular attention, after a three-year follow-up period, to the postphlebitic syndrome: swelling, edema, skin induration, skin atrophy and leg ulcers. Bauer found that practically 100 per cent of those patients who had been treated by conservative therapy had swelling of the affected leg while only about one-quarter of the heparin-treated group had swelling of the leg; that approximately 75 per cent of the conservatively treated group had some degree of trophic skin changes and induration, one-quarter of them having very marked trophic changes. The heparin-treated group showed none of these skin changes. With regard to ulceration of the lower legs, 20 per cent of the conservatively treated group had leg

ulcers at three years. There were no leg ulcers in the heparin group at the three-year follow-up period.

DR. FRANKLIN M. HANGER: Dr. Cosgriff, would you tell us exactly how your group advises that thrombotic or embolic cases be managed?

DR. COSGRIFF: The program of management of a case of thrombosis or pulmonary embolism at the present time may be outlined as follows: The patient is placed in bed on strict bed rest for approximately six days. Anticoagulants are started immediately. If on the sixth or seventh day the patient is in good condition, the vital signs are normal and the pulmonary status as well as the leg signs are satisfactory, the patient is ambulated progressively, still maintained on anticoagulants. If by the twelfth or thirteenth day the patient is completely ambulatory, seems to be doing well and the signs of active venous thrombosis have cleared anticoagulant therapy is discontinued. With dicumarol there is a lag period of several days before the prolonged prothrombin time returns to normal so that an anticoagulant effect will persist for this period. Approximately by the fourteenth or fifteenth day the prothrombin time is within normal limits, the patient is completely mobilized and is released from our management.

We use a combined heparin and dicumarol program, with dicumarol as the principal drug. Since dicumarol usually has a twenty-four to forty-eight-hour lag period, heparin is employed during this preliminary period to obtain an immediate anticoagulant effect at the start of the dicumarol treatment and also at any time during the course of dicumarol treatment when the prothrombin time elevation drops below what we consider an effective level. At such times we give supplementary heparin for twelve to twenty-four hours until the prothrombin time elevation is again satisfactory.

Dicumarol is given orally, once daily. The first dose is 300 mg. On the second day the patient usually receives 100 or 200 mg. The average daily maintenance dose is usually 50 or 100 mg. This is given *only after the*

daily prothrombin time has been determined and the results reported to the physician responsible for anticoagulant regulation. The rectal route of administration has been investigated here and three or four patients have been treated in this manner with successful results. However, the usefulness of that route of administration needs more confirmation.

As determined in the laboratory of the Presbyterian Hospital, the prothrombin time normally is 14 (± 2) seconds. An elevation to 22 seconds, which is 30 per cent of normal prothrombin activity, is believed to be the level above which further intravascular thrombosis will not occur. The range between 22 and 45 seconds (45 seconds is 10 per cent of normal prothrombin activity) is the effective and yet safe range. Bleeding rarely occurs with prothrombin times below 45 seconds; many individuals have elevations in prothrombin time above 45 seconds without experiencing any difficulty; however, hemorrhage will almost invariably occur only in the group which rises above the critical level.

In gauging the dose of dicumarol, the physician should remember that he is estimating the dose for an effect twenty-four to forty-eight hours in the future. After stopping the drug it should likewise be borne in mind that dicumarol may continue to exert an effect for two to seven days.

It should be noted that approximately 15 per cent of patients are significant hyper-reactors to dicumarol and will develop excessive elevation of prothrombin time with the usual dosage. This emphasizes the necessity for frequent and reliable prothrombin time determinations.

As regards the dose of heparin, the venous clotting time is maintained between 20 to 40 minutes, the normal range being 5 to 10 minutes. We administer heparin in two principal ways. The first is by continuous infusion of 100 mg. of heparin in 1000 cc. glucose or saline solution at the rate of about 25 drops per minute; the second route is by repeated subcutaneous injection of heparin in doses averaging 30 mg. every three hours.

This second route has been employed in the majority of our cases and we have found it especially practicable since the heparin administration can be carried out by the nursing staff and does not demand the attention of the physician. Although some groups believe that control of dosage by venous clotting time determination is not necessary, we believe that the venous clotting time should be estimated at least once and preferably twice a day to insure safety.

Anticoagulant therapy would appear to be indicated in deep venous thrombosis, pulmonary embolism, embolic phenomena of intracardiac origin, prophylactically in individuals with a history of previous thromboembolism, following arterial occlusion and in recalcitrant superficial phlebitis. There are a few situations in which we do not usually employ anticoagulants. We are reluctant to do so when a central nervous system operation has been performed recently, in subacute bacterial endocarditis, except when embolic arterial occlusion has occurred, in hemorrhagic blood dyscrasias, in recent threatened abortion when a viable fetus is desired and in obstetrical cases within six weeks of the estimated date of delivery. Careful consideration should be given to the group of cases in which anticoagulants, although not contraindicated, should be used cautiously. First, are patients with liver disease, for such patients may be deficient in the elaboration of prothrombin; second, renal insufficiency, for it is believed that dicumarol and heparin both are excreted in some form by the renal route; third, patients with an open ulcerating wound, since granulating surfaces certainly tend to bleed more easily than do intact wounds which are completely closed; fourth and fifth, individuals with malnutrition and those who are very old since they are likely to hyper-react to anticoagulants. It is believed that this group may be given anticoagulants if necessary but only with special precautions; individuals in this latter classification have been given anticoagulants at this hospital without untoward results.

DOCTOR: What about the toxic and undesirable side effects produced by the anti-coagulants? How should they be handled?

DR. COSGRIFF: Hemorrhage is about the only real toxic manifestation of the anti-coagulants. Statistics on the incidence of bleeding during heparin treatment are rather infrequent in the literature; we have experienced it in about 1 per cent of our group. As regards dicumarol, the Mayo Clinic's figures are the most extensive. They encountered mild bleeding in about 2.5 per cent of their dicumarol-treated patients and major hemorrhages in another 2 or 2.5 per cent. In our group mild bleeding was encountered in 2 per cent of those treated with dicumarol.

As to the management of hemorrhage occurring in the course of heparin treatment, the drug is discontinued at once and a transfusion of blood or plasma is given. This does not reduce the clotting time precipitously to normal but does return it toward the safer range. It is reported that administration of protamine sulfate (5 to 10 cc. of a 1 per cent solution) will return a venous clotting time, which has been excessively prolonged by heparin immediately to normal. However, this treatment has not been used by our group.

As regards bleeding occurring with dicumarol, first stop the drug, then administer synthetic vitamin K (menadione bisulfite) in massive dosages of 60 to 75 mg. parenterally. Reports in the literature and our own experience indicate that this dosage of menadione will return an excessively elevated prothrombin time to within the safe range in approximately 85 per cent of the patients within twelve to forty-eight hours following administration. It should be emphasized that there is no certain method for predicting if and how rapidly an individual will react to vitamin K other than by following the prothrombin time carefully at intervals of six to twelve hours until the desired effect is produced.

In bleeding during dicumarol therapy one should aim at obtaining an immediate reduction of prothrombin time. This may

be done by the use of whole blood or plasma. We have had the most experience with the administration of 500 cc. of reconstituted lyophilized plasma which reduces the prothrombin time from the excessively elevated dangerous levels to within safe limits immediately after administration. Such a reduction is maintained for approximately six to ten hours, at which time the prothrombin time has returned toward that present before the administration of the plasma. Therefore, when bleeding is taking place plasma should be administered at once in order to obtain an immediate effect and should be repeated several times at proper intervals until prothrombin time determinations indicate that the synthetic vitamin K which was given has permanently returned the prothrombin time to safe limits. The risk of possible serum hepatitis must be considered when the decision to employ plasma is made.

As to the general management of a patient, we believe in *complete* bed rest. This entails lying quietly in bed, no undue active motion, no leg exercises, no massage and no straining on the bed pan and analogous efforts. Dr. Linton at the Massachusetts General Hospital determined the venous pressure in the lower extremity veins in individuals before and during performance of the Valsalva experiment, which is analogous to straining on the bed pan, at which site many people have been known to die from pulmonary emboli. He found that the venous pressure in the lower extremities was raised as much as four times the control level during this effort. It is not difficult to visualize the distention which occurs in the deep veins of the extremities and in the pelvis under such circumstances and the effect that this might have on loosening thrombi from the vein wall.

The foot of the bed is usually elevated to 15 degrees thus encouraging venous return and preventing undue stasis.

If pulmonary embolization has occurred, digitalization has been freely employed for any signs of cardiac failure or acute cor pulmonale. Dr. de Takats has shown in dogs that a pulmonary embolus produces bron-

chospasm, pulmonary artery spasm and changes in cardiac rhythm and coronary flow. The mechanism of such changes may be partly vagal reflexes. These effects were decreased by atropine and papaverine. We believe at the present time that, in patients with large pulmonary emboli, papaverine and atropine may help. We have been employing papaverine, 60 mg. intravenously every four hours, for the first thirty-six hours. Atropine has been given in doses of 1 mg. intravenously or intramuscularly every four hours for this same period.

Oxygen has been employed freely. When severe pleuritic pain has been present and not controlled by the usual measures, intercostal nerve block frequently has been effective in reducing or completely removing that complaint.

Now a word as to the philosophy of the use of anticoagulants in general. Any physician who intends to use anticoagulants should have at his ready disposal proper control of these drugs. The dosage of heparin is properly controlled at the present time by a venous clotting time determination done at least once and preferably twice a day. The effect of dicumarol must be controlled by a prothrombin time determination done daily. We believe that the danger of bleeding in anticoagulant therapy is very real and that careful control and supervision is imperative. If carefully controlled, however, we believe that the *proper* employment of anticoagulants is safe and the most important procedure in the management of thromboembolism.

DR. KNEELAND: Two weeks ago I was participating in a symposium on infectious diseases at a famous university clinic and one of the staff members presented the case record of a patient with pneumococcus meningitis. As he was describing the various clinical phenomena and what was done about them, he said "And of course on the second day of hospital admission we did a bilateral femoral vein ligation. As we all know in a situation like this, where a patient is in bed with a high fever, dehydrated and very ill, he is likely to develop phle-

bothrombosis and subsequently pulmonary embolism."

That was a rather surprising statement to me because of the casual way in which it was interjected into the case history as part of a routine procedure which everyone naturally would take more or less for granted. It indicated, however, that there is another school of thought on the management of these conditions. I should like to ask Dr. Habib to present his views in regard to vein ligation.

DR. DAVID V. HABIB: As has been pointed out previously, the aim of treatment of thrombosis of the deep veins of the lower extremity is to prevent a fatal or non-fatal embolus; to prevent progression of the disease by limiting its propagation proximally, distally and into the small radicles of the calf; to further more rapid subsidence of the process than occurs with conservative treatment; to shorten convalescence and, in so far as possible, to prevent or lessen the edema, pain, varices and ulcers which occur in the postphlebotic syndrome.

The prophylactic measures which are carried out in the surgical services are many: Sharp dissection with careful hemostasis, avoidance of tight dressings, tight abdominal binders and tight tourniquets on the legs, elevation of the legs with leg and body exercises, frequent turning of the patient, encouragement of deep breathing, the use of CO₂ to aid in deep breathing and in the prevention of atelectasis and pneumonia and early mobilization (which means walking on the first postoperative day). We have come to frown upon allowing a patient out of bed the first postoperative day only to sit in a chair. We believe that the resultant stasis is perhaps worse than having the patient in bed. It has been found that prolonged immobilization will lead to a higher incidence of thromboembolism; in our own clinic, the incidence of thromboembolism in 500 patients treated with the usual ten to fourteen days of postoperative bed rest was 2.4 per cent compared with 1 per cent in 500 patients treated with early mobilization. Others, however, have reported no change in the incidence of phlebothrombosis or

embolus with bed rest as compared with early mobilization.

STUDENT: When in the postoperative period is thrombosis or embolism most apt to occur?

DR. HABIF: Phlebothrombosis commonly manifests itself between the fourth and fourteenth day after operation but may occur as early as the second or third day and any time thereafter.

We are especially interested in the long veins of the leg and the pelvis since we know that emboli arising elsewhere are usually non-fatal. The process is believed to start in the veins of the feet, progress to the calves, then up to the thigh into the iliac veins. The three most common types we see on the surgical service are phlebothrombosis, or thrombophlebitis of the calf, severe ilio-femoral thrombophlebitis and pulmonary embolus without an obvious source.

The arguments of the advocates of surgery for ligation of the superficial femoral and the common femoral veins are that the operation is simple, that it can be done under local anesthesia and that the operative mortality is almost zero. The course of the disease is altered in that the pain and the inflammatory process subside more rapidly with removal of the thrombus and convalescence is shortened, the average return to health being reduced to four and one-half days. The patient can be released from the hospital within eight and one-half days. Femoral vein ligation protects from added morbidity and eliminates the chance of a fatal embolus. Phlebitis treated with anticoagulant therapy manifests itself after stopping the anticoagulant therapy and infarcts have been reported to occur after the prolonged use of heparin when the heparin was stopped.

The indications set down for bilateral ligation are the presence of a venous thrombosis in the deep veins of the lower extremity; the occurrence of a non-fatal pulmonary embolus irrespective of whether or not the legs show signs of thrombosis; a concomitant rise in temperature, pulse and respirations postoperatively in a patient in whom these symptoms cannot be explained by some

other cause; unilateral thrombosis even though there are no signs in the opposite leg (it is well known that at least 30 per cent of patients with unilateral symptoms will show thromboses in the opposite leg although no symptoms appear there); prophylactically in patients over fifty subject to major surgical procedures, particularly abdominal and pelvic; patients with carcinoma; following hip fractures (especially intertrochanteric) and prostatectomy. The older the patient the more likely a fatal embolus. The operation can be done prior to the major procedure or at the same time.

Now what are the arguments against surgery? It is an operation and it will be done needlessly at times. However, ligation or removal of a segment of the superficial femoral vein of a normal leg ordinarily causes no disturbance. Ligation of the common femoral vein is at times associated with profound shock, the mechanism of which is not clear, and we have had one death in this clinic from ligation of a common femoral vein. The edema of the affected leg often is increased, especially after common femoral vein ligation. Such edema appears early and may be marked but eventually decreases. A high percentage of the ligated group are found to have mild edema one year following the procedure and there is no opportunity to recanalize. However, there is some argument about whether one should recanalize, some groups believing that persistent total blockage of the vein will lead to better collateral circulation.

Five per cent of those who have a bilateral superficial vein ligation have been reported to have subsequent non-fatal pulmonary emboli, necessitating treatment with anticoagulant therapy. The thrombus may appear above the point of ligation as well as progressing distally. Surgery does not take care of the emboli arising in the heart. There is a fear of dislodging the thrombus as the result of introduction of a cannula proximally to the point of incision in the vein. There is an incidence of wound infection slightly less than 2 per cent.

The operation is best done within forty-eight hours of the detection of the thrombosis. The classical case for ligation is the one in which the process is confined below the knees, especially in the calf veins. A vertical incision is made, as recommended by the Boston group, 1 inch above the groin for a total of 3 inches directly over the femoral artery. The lymph nodes, lymphatics and femoral artery are retracted laterally and the saphenous vein medially. A ligature is placed about the common, deep and superficial veins. If the common vein is thrombosed, it is opened. The thrombus is aspirated and the common femoral vein ligated. If the common femoral vein is normal, the superficial vein is opened, aspirated with a rubber catheter or glass cannula up to the bifurcation of the vena cava and then ligated. Bleeding must be free. If you have an older patient with poor collateral circulation and absence of pulses in the feet, ligation of the common femoral with the internal saphenous is not advised. In this clinic we prefer the superficial femoral vein for several reasons. One, we frown upon common femoral vein ligations because of the possibility of shock and death; two, the exposure is more difficult because of the collateral circulation of the common femoral vein. It is short and cannot be divided easily. One enters the lymphatic area and there is occasionally a collection of lymphatic fluid in the wound postoperatively. The superficial femoral vein nearing its junction with the profunda has few tributaries and its exposure is quite easy.

Some surgeons throughout the country have advocated ligation of the iliacs and the inferior vena cava. This requires an abdominal incision and a general anesthetic. The argument for inferior vena cava ligation is that an iliac ligation has to be bilateral; if one has a patient with thrombophlebitis of the iliac veins giving off repeated emboli, with or without a previous femoral vein ligation, vena cava ligation may be justified. At present, we do not agree with the protagonists of inferior vena cava ligation, believing that such a major procedure should

be avoided by anticoagulant therapy which adequately obviates any further emboli.

As to axillary and saphenous thromboses, it is well known that the incidence of emboli from these sources is very small. Prior to the use of anticoagulant therapy, we ligated the saphenous vein occasionally.

DOCTOR: What are the principles of management of suppurative thrombophlebitis?

DR. HABIF: Vein ligation proximal to the process is mandatory. Moreover, remember that in the case of pelvic vein involvement, not only is the vena cava ligated but both ovarian or spermatic veins. It is believed that anticoagulant therapy may be of value following ligation; however, our group has had no experience with this problem.

On the surgical service "leg rounds" have now become routine, like "sleeping pill rounds" and "carthartic pill rounds." One must appreciate the high incidence of thrombi producing no clinical symptoms whatever and that at least 50 per cent of older people harbor small segments of thrombi in the veins of the feet, legs and calves. It is important not to overlook a deep vein thrombosis in the presence of an obvious internal or external saphenous vein phlebitis.

If an adequate organization for the control of anticoagulant therapy is not available and the patient is in the hospital, then we think ligation is indicated. At present, we do not believe that ligation is the answer to the problem and until a simple, effective prophylactic means is found anticoagulant therapy seems more rational and gives excellent results.

Before closing this discussion of surgical indications in thromboembolism I should like to say something about lumbar sympathetic block. Any vascular occlusion will produce vasospasm in the collateral vascular bed and in adjoining major vessels when they are in the same vascular sheath. Pain and edema are due in part to vasoconstriction. The degree of vasospasm seems to be proportional to the perivascular involvement and the exudate around an acute thrombophlebitis. There is pain, a sense of

constriction. The limb is cold, slightly blue, with diminished or absent arterial pulsations. To combat this situation, lumbar block was first advocated by Leriche and Cournand and popularized by Ochsner and DeBakey. The procedure involves blocking the first, second, third and fourth lumbar ganglia with 1 per cent procaine. It does relieve the pain, most often dramatically, although this may be transitory and the block must be repeated once or twice again. It relieves the vasospasm, allowing for compensatory venous circulation of the affected limb, and it relieves the edema. It restores the arterial pulsations and, in the majority of cases, the process subsides rapidly. A severe degree of vasospasm is usually seen, however, only in the extreme cases of acute thrombophlebitis and we have had few cases requiring lumbar block.

SUMMARY

DR. FREDERICK K. HEATH: The common denominator, prerequisite to an understanding of the mechanisms upon which present day therapy of thromboembolism is based, is the increased tendency of the blood to clot. This may be demonstrated by the Lee-White method of determining the clotting time by which, if lucite or paraffin coated tubes are used, an actual decrease in coagulation time below the normal may be noted. Why the blood tends to clot faster is not known but poor muscle tone, venous stasis and tissue damage seem to be predisposing factors.

At any rate, clotting occurs and a thrombus is formed. In about 90 per cent of instances, this develops below the inguinal ligaments, most frequently in the deep veins of the calf. Early in its evolution no signs or symptoms are found. As the clot grows, inflammation of the vein wall, representing the reparative phase, may result in tenderness; obstruction of the vein may produce mild edema of the tissue drained. With growth of the 'tail' to involve larger veins, more venous obstruction and more edema may result until, with adherence of the 'tail,' definite venous obstruction is present and

swelling of the calf ensues. At this juncture a considerable inflammatory reaction is present producing the common findings of pain, tenderness, fever, leukocytosis and elevation of the sedimentation rate. When these are marked, vasospasm may also occur. The typical picture is now one of acute thrombophlebitis as described by Ochsner. When the inflammatory process is less severe, or perhaps earlier in the course, the pattern resembles phlebothrombosis. Whether more profound differences exist between these clinical entities is not yet clear.

The rate of healing is variable but takes place first by adherence of the clot and its 'tail,' which occurs about the fifth day, and then by endothelialization, completed by the tenth to twelfth day if growth can be prevented. These time factors are important not only because upon them is based the duration of anticoagulant therapy but also because they suggest when ligation is most needed.

The breaking-off of the thrombus or its 'tail' before these are adherent, with consequent pulmonary embolization, is a major event in the pathologic sequence and may produce a dramatic clinical picture. Again this aspect is variable, ranging from small emboli producing mild pleuritic pain with no signs to massive embolization causing sudden death. Between these extremes, deep constant pain, cyanosis, reflex dyspnea, cough and hemoptysis (rather infrequently), râles and, occasionally, pleural effusion may be encountered. Serious impairment of the pulmonary arterial flow and an accentuated pulmonic second sound may herald right heart failure and electrocardiographic evidence of acute cor pulmonale; nor should the presence of abdominal findings of pain and muscular spasm fail to suggest the possibility of a basal infarct with diaphragmatic irritation. The appearance of signs or symptoms referable to the lungs or pleura should always call to mind the possibility of thromboembolism.

The aim of anticoagulant therapy is to prolong blood coagulation so as to prevent further growth of the thrombus in the vein of

origin. If this can be done, the thrombus will become adherent and repair may take place before the 'tail' breaks off to become an embolus. When embolization has already occurred, the aim is not only to attain the same end at the original site so as to prevent further potential embolus formation but also to prevent proximal propagation of the thrombus which forms behind the embolus lodged in the lungs. This is carried out by the use of heparin and dicumarol with daily careful clotting and prothrombin time determinations. Statistics indicate that the results of anticoagulant therapy are excellent both in achieving a favorable local result as well as in preventing pulmonary embolization or its recurrence. Fatal pulmonary embolization, subsequent pulmonary embolization and venous thrombosis have each been reduced to about 1 per cent. Hemorrhage has been the only serious toxic manifestation of anticoagulant therapy. It is infrequent with adequate control and can

be successfully combatted by the use of plasma and blood, and by vitamin K when dicumarol is the anticoagulant.

Contraindications to anticoagulants exist: subacute bacterial endocarditis, hemorrhagic blood dyscrasias, recent threatened abortion, obstetrical cases near term and after a recent central nervous system operation. Anticoagulants obviously cannot be used prophylactically in the immediate pre-operative period. They should be used with caution in liver disease or renal insufficiency and in patients with ulceration or malnutrition and in very old patients.

At the present time, bilateral ligation of the femoral vein distal to the point of entry of the deep femoral vein is the surgical approach of choice. No obvious advantages can be expected from this mode of therapy which make it superior to anticoagulants. It is therefore usually reserved for situations in which anticoagulant therapy cannot be used.

Clinico-pathologic Conference

Cardiac Disease with Cardiac Insufficiency and Peripheral Vascular Complications*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. A., a forty-two year-old married Negro truck driver, entered the Barnes Hospital on May 15, 1946, complaining of shortness of breath and swelling of the abdomen and lower extremities. The family history was not known; in regard to the past history, the patient maintained that he had been in good health all of his life but his wife stated that he had had one attack of rheumatic fever and had a "leaky heart" for some years. Otherwise, no significant illness was known and the systemic history was essentially negative. The patient had been married four times. For years he had worked as a laborer, truck driver or at other jobs which entailed strenuous exertion. He neither drank nor smoked.

In 1941, the patient applied for a defense job; he was told that he had a "bad heart" and was rejected. He had no cardiac symptoms, however, until the spring of 1945, when he first noticed shortness of breath on exertion which was soon followed by an intermittent non-productive cough. Three or four months later, he had his first attack of severe shortness of breath at night, subsequently, paroxysmal nocturnal dyspnea recurred with increasing frequency. Shortly after the first attack, swelling of the ankles was noted, particularly in the evening, and the patient was advised by his physician to take two weeks rest in the hospital. He disregarded the advice and continued to work.

All of his symptoms increased in the next two months and ankle edema became persistent. He was given digitalis and mercurpurin and the swelling of the legs and shortness of breath decreased.

Five months prior to admission, he was told for the first time that his blood pressure was elevated; his physician stated that the reading was "220"; the patient continued to take digitalis daily and he received injections of mercurpurin every two or three days. Despite these measures, the swelling of the lower extremities gradually progressed and his abdomen began to swell; concomitantly, there was marked diminution in urinary output. In the month before entry, the patient continued to work but his symptoms increased rapidly during this period.

At the time of admission, the physical examination revealed the temperature to be 37.7°C., pulse 120, respirations 20 and blood pressure 194/155. The patient was a well developed colored male who was in acute respiratory distress. His skin was cold and moist and the nail beds were cyanotic. The pupils were small and reacted normally to accommodation but not to light; the sclerae and conjunctivae were clear. Examination of the fundi revealed the arterioles to be very narrow and tortuous; a few exudates were seen but no hemorrhages were present. No abnormalities were noted in the upper respiratory tract. On percussion of the chest, there was dullness at both lung bases

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posteriorly; over these areas, tactile fremitus was decreased and medium moist râles were audible. Breath sounds were of good quality throughout. Cardiac dullness extended 16 cm. to the left of the midsternal line in the fifth interspace and 7 cm. to the right in the fourth interspace. A grade II systolic murmur was heard over the apex and a proto-diastolic gallop rhythm was audible over the entire precordium. The abdomen was distended and signs of ascites were prominent. The liver dullness was percussed 4 cm. below the right costal margin but the edge was only questionably palpable. Four plus edema extended up to the iliac crests and involved both the penis and scrotum. The neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 6,420,000; hemoglobin, 17 Gm.; white cells, 10,650; differential count: eosinophiles, 1 per cent; stab forms, 5 per cent; segmented forms, 68 per cent; lymphocytes, 21 per cent; monocytes, 5 per cent. Urinalysis: albumin, 3+; sediment, negative. Stool: guaiac, negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 33 mg. per cent; total blood protein, 6.2 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 3.0 Gm. per cent. Venous pressure: 255 mm. NaCl. Circulation time (decholin): 45 seconds. Corrected sedimentation rate: 0.3 mm. per minute. Electrocardiogram: Low voltage in leads II and III; S-T segments depressed in leads I and II; Q wave in lead C-F IV; left axis deviation. Roentgenogram of the chest: "There is second degree cardiac enlargement and fluid is present in both pleural cavities."

On entry, the patient was placed in an oxygen tent and given morphine, aminophylline and digitalis. His general condition improved somewhat but, due to the marked edema of the penis, he was unable to void. Twenty-four hours after admission, he was catheterized and subsequently there were no urinary difficulties. Digitalis had very little effect on the pulse rate and oral ammonium chloride combined with intra-

venous mercupurin were used as diuretics with only moderate effect. From the outset, the patient had a low grade, spiking temperature. The fever was believed to be due to a urinary infection for beta-hemolytic streptococci were cultured from the urine repeatedly; although no white cells were noted in any of the urine specimens examined, penicillin therapy was instituted.

On the fifth hospital day, the patient's respiratory difficulty had improved sufficiently to warrant his being taken out of the oxygen tent. He continued, however, to have orthopnea, edema and ascites; likewise, tachycardia and the gallop rhythm persisted. One week after entry, he had an episode of substernal pain of mild to moderate severity which was relieved by nitroglycerine and aminophylline. Two days later he complained of pain, numbness and tingling of both feet and was given papaverine intravenously. One hour later, he was found in a state of apparent peripheral vascular collapse with Cheyne-Stokes respirations; he was revived by adrenalin and coramine given intravenously. The following day, he developed pain in the right leg and tenderness over the right calf was elicited. The temperature, which had ranged between 37° and 38°C., rose to levels between 38° and 39°C. for several days. The right foot became cold and gangrenous and discoloration of the skin extended up to the mid-thigh. A paravertebral sympathetic block with novocaine was performed and heparin and dicumarol therapy were begun. Neither favorably influenced the course of the gangrene. Repeat electrocardiograms showed no essential change from the record obtained on admission. The icteric index rose to 20 units but fell to normal within a few days. Repeat urinalyses were all normal except for the appearance of an occasional cast. The non-protein nitrogen at the time of development of gangrene rose to 50 mg. per cent but it, too, fell rapidly to normal. The white blood count was 20,000 and the sedimentation rate rose to 1.2 mm. per minute. Dicumarol therapy lowered the prothrombin time to 33 per cent of normal.

The patient developed a generalized erythematous scaling skin eruption thought to be due to penicillin sensitivity; he was given benadryl and penicillin was withdrawn. He continued to do poorly; the tachycardia and gallop rhythm persisted. The signs of fluid at the right lung base increased as the patient became disoriented and his respirations gradually grew more labored. On the day before his death, his temperature rose to 40.3°C. and the following day pain in the right leg, which had subsided somewhat, again became severe. The patient expired quietly on June 8, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents us with the opportunity of discussing certain phases of cardiac failure and its complications. It would seem important that we first attempt to establish the etiology of the heart disease which this patient certainly had. The history in this regard is rather confusing. The patient's wife stated that he had rheumatic fever at one time and a "leaky heart" for years. The patient, on the other hand, stated that he first became aware of cardiac disease five years before entry; at that time, when he was thirty-seven years of age, he was rejected when he applied for a defense job because of a "bad heart." Dr. Massie, from the evidence at hand, what is your opinion as to the type of heart disease with which this patient was afflicted?

DR. EDWARD MASSIE: I would say unhesitatingly that he had hypertensive cardiovascular disease.

DR. ALEXANDER: Do you believe that when the pathologist presents his findings he will describe a lesion of the mitral valve?

DR. MASSIE: No, I do not.

DR. ALEXANDER: Dr. Smith, what is your opinion?

DR. JOHN R. SMITH: I agree with Dr. Massie that this patient did not have rheumatic heart disease. I would add however to the diagnosis of hypertensive cardiovascular disease that of coronary artery disease.

DR. ALEXANDER: Seemingly, the patient

had some evidence of heart disease at the age of thirty-seven when he was rejected for a defense job. Despite this fact, he continued to work until a month or so before entry to the hospital. Is such a history compatible with rheumatic heart disease?

DR. MASSIE: If he had had rheumatic heart disease with minimal mitral insufficiency, he could have led a perfectly normal life. The murmur was described as grade II and apparently was not very intense; such a finding is compatible with mitral insufficiency of only moderate degree. We are handicapped in our interpretation by the fact that, although we are told that five years before entry the patient had a "bad heart," we know nothing of his blood pressure until five months or so before he died.

DR. ALEXANDER: It seems remarkable that he was able to do heavy physical labor almost up to the time he came into the hospital. If the etiology of the heart disease were rheumatic, would it have been likely that the patient could have worked as long as he did?

DR. MASSIE: If he had had mitral stenosis, I would agree that it is unlikely that he could have gotten along so well for so long a period; on the other hand, I still believe that the history is compatible with moderate mitral insufficiency and no stenosis.

DR. ALEXANDER: What about the episodes of paroxysmal nocturnal dyspnea? Are these of importance in differential diagnosis?

DR. MASSIE: To some extent they are; paroxysmal nocturnal dyspnea is more frequently seen in association with hypertensive cardiovascular disease than with rheumatic disease.

DR. ALEXANDER: Is there agreement with the views expressed by Drs. Massie and Smith; namely, that the pathologist will report cardiac enlargement, hypertrophy and perhaps involvement of the coronary vessels but no rheumatic valvulitis?

DR. W. BARRY WOOD, JR.: I do not see how such a view can be accepted if one considers the past history. How can hypertensive cardiovascular disease explain a "leaking heart" for many years? How can

coronary artery disease do so? Although there is considerable evidence for both of these diagnoses, they will not explain the past history *in toto*. One either has to disregard the past history or else one has to postulate a lesion or lesions which would cause such physical signs.

DR. WILLIAM H. OLMSTED: How reliable is the past history?

DR. ROBERT J. GLASER: I can say that those of us who spoke to the patient's wife believed that she was a very intelligent woman and a good observer. The patient was, of course, critically ill when he was admitted and the history which he gave may well be open to question; we were all quite convinced, however, that his wife was a dependable informant.

DR. EDWARD H. REINHARD: Is it not possible that this patient had other murmurs prior to his terminal episode which disappeared with the onset of severe decompensation?

DR. MASSIE: If the patient had been fibrillating, I could understand the absence of a diastolic rumble, particularly of the presystolic phase; likewise, if auscultation was not repeated frequently, such a murmur might not have been heard but this patient had a regular rhythm and I am sure that he was subjected to repeated careful cardiac examination. Therefore, I would hesitate to believe that the murmur was missed.

DR. ALEXANDER: The heart was quite huge, was it not? It was described as being enlarged to both the right and left. Would such enlargement commonly occur in pure hypertensive cardiovascular disease? It is recorded that the systolic blood pressure was only 194 mm. of Hg.; of course, that reading was taken during marked failure and an earlier reading was said to have been 220 mm. of Hg. Would the presence of rheumatic valvular involvement better explain the size of the heart or does not this point disturb you in your interpretation?

DR. MASSIE: I do not think that rheumatic involvement need be postulated to explain the heart size; I believe it is compatible with hypertensive cardiovascular disease in

its more advanced phase and in this case the process was indeed advanced:

DR. ALEXANDER: Dr. Bottom, did the cardiac x-ray findings suggest mitral heart disease to you?

DR. DONALD S. BOTTOM: No. The aorta was somewhat prominent and seemed more consistent with a diagnosis of hypertensive cardiovascular disease. When a heart is so markedly enlarged and cardiac failure has ensued, it is impossible to make a definitive x-ray diagnosis. We cannot rule out mitral disease in this particular case.

DR. VIRGIL C. SCOTT: I would appreciate Dr. Bottom's explaining what the radiologist means by the term, "second degree cardiac enlargement."

DR. BOTTOM: There are three degrees of cardiac enlargement according to the radiologist's classification: second degree enlargement indicates that the left cardiac border extends to the mid-portion of the left lung and that the enlargement to the right is such that the entire cardiac shadow takes up about 70 per cent of the total intrathoracic diameter. In third degree enlargement, the left border extends to the chest wall at the inner margin of the ribs and right sided enlargement is also marked.

DR. ALEXANDER: All of us, I think, will agree that the patient had hypertensive cardiovascular disease; we still have not settled the question as to whether, in addition, he had rheumatic heart disease. Is there anything else, Dr. Wood, beside the history which you would like to emphasize in this connection?

DR. WOOD: No, except to mention the point that Dr. Levine in Boston has frequently made, namely, that patients who have mitral disease and subsequently develop hypertension often do well. I do not know if the cardiologists here accept Dr. Levine's views in this regard.

DR. MASSIE: If the hypertension is moderate, I agree that it may favorably effect the patient's course.

DR. SCOTT: I would like to ask Dr. Massie about the polycythemia recorded in this case. Usually in cardiac failure, pa-

tients have hemodilution and the red count and hemoglobin are relatively low.

DR. MASSIE: I would like to refer Dr. Scott's question to Dr. Carl Moore.

DR. CARL V. MOORE: The red blood cell count recorded here could be a perfectly normal one for a robust male but there is one other possibility which would explain the elevated red blood cell count. This man was cyanotic on admission. If the cyanosis had been present for a matter of ten days or two weeks, he could have developed relative polycythemia in spite of the fact that he was in cardiac failure.

DR. ALEXANDER: Let us now go on to the apparent arterial occlusion. Was it a thrombus or an embolus?

DR. HENRY A. SCHROEDER: I think it was most likely an embolus, probably arising from a mural thrombus in the heart. The only flaw in such an explanation lies in the fact that the electrocardiograms did not exhibit the characteristic changes of coronary occlusion.

DR. ALEXANDER: Dr. Smith, what cardiac abnormalities are apt to give rise to arterial emboli?

DR. SMITH: Three are usually mentioned: First, subacute bacterial endocarditis; second, mural thrombi secondary to a myocardial infarction which involves the endocardium and third, mural thrombi which arise in the presence of auricular fibrillation.

DR. ALEXANDER: What is the order of frequency of the three?

DR. SMITH: I would think of myocardial infarction first, then of auricular fibrillation and lastly, subacute bacterial endocarditis; none of these is uncommon and the history and physical findings often cast considerable light as to which is responsible for a given arterial occlusion.

DR. ALEXANDER: It was my impression that arterial emboli occur most commonly as a complication of auricular fibrillation.

DR. MASSIE: I think that Dr. Smith was considering the older age group. If one were to consider a group of patients under forty, auricular fibrillation would be associated

with mural thrombi and arterial emboli more frequently than would myocardial infarction; on the other hand, in a group of patients above forty the converse would be true.

DR. ALEXANDER: Thank you, Dr. Massie, for clarifying this point. In the case now under discussion, the history states that two days before the patient developed numbness and tingling in his feet he had substernal pain relieved by nitroglycerine. If the substernal pain actually represented a myocardial infarction, is forty-eight hours a sufficient interval for the formation of a mural thrombus?

DR. SMITH: I believe it is rather short.

DR. ALEXANDER: How long a time would you expect to be necessary for the formation of a thrombus?

DR. SMITH: Usually, mural thrombi develop a week or so after the infarction occurs.

DR. ALEXANDER: Would you consider the possibility that a soft clot may have formed within forty-eight hours of an infarct?

DR. SMITH: I think it more likely that the patient had an old myocardial infarct with a mural thrombus which became detached.

DR. ALEXANDER: This man had definite vascular stasis; his venous pressure was very high and his circulation time was prolonged. Would you care to entertain the possibility that the arterial occlusion was due to a thrombus rather than to an embolus?

DR. SMITH: I think not.

DR. ALEXANDER: Here, except for the fact that the time interval seems short, the case for a myocardial infarction with formation of a mural thrombus and subsequent arterial embolization seems strong. The sedimentation rate began to rise three or four days after the episode of chest pain and one or two days after the temperature had risen above its previous level. Would you comment on the importance of these changes, Dr. Moore?

DR. C. V. MOORE: In the majority of patients with myocardial infarction, there is a temperature elevation commonly within twenty-four to forty-eight hours and very

shortly thereafter the sedimentation rate likewise rises. In this case, the lag between the infarction and the rise in sedimentation rate is somewhat longer than is usually encountered.

DR. MASSIE: Dr. Moore's statement concerning the rise in sedimentation rate within forty-eight to seventy-two hours of a myocardial infarction holds in most cases, I think, but it is important to point out that in occasional instances the sedimentation rate after massive infarctions may increase only after quite a considerable period has elapsed; we have seen the rise come as long as ten to fourteen days after the acute episode.

DR. ALEXANDER: It seems that there is little doubt that this patient had a myocardial infarction and a subsequent arterial embolus. Where do you think the peripheral occlusion was, Dr. Schroeder?

DR. SCHROEDER: Probably at the origin of the femoral artery.

DR. ALEXANDER: This man first had bilateral parathesias and later unilateral pain, Dr. Schroeder. Would you comment on the pain and also discuss the usual site of an embolus? Also, what is the status of embolectomy?

DR. SCHROEDER: First of all, there is usually considerable spasm associated with arterial occlusion and it is believed that the pain is at least, to a large extent, associated with the spasm. The embolus is usually located at the bifurcation of the artery for that is where the vessel narrows. If embolectomy is contemplated, it must be done without delay for not only may irreversible changes occur in the tissues supplied by the occluded vessel but also extensive thrombosis of the artery, distal to the embolus, may develop.

DR. ALEXANDER: May spasm *per se* be injurious?

DR. SCHROEDER: Spasm may contribute to decreased collateral circulation which affords the only source of blood supply to the limb distal to the embolus.

DR. ALBERT ROOS: I should like to suggest that thrombophlebitis of the femoral vein

rather than arterial embolism may have occurred in this patient. I remember a case in which, at post mortem examination, only thrombophlebitis of the femoral vein was demonstrated but which clinically had presented the typical manifestations of femoral arterial obstruction.

DR. ALEXANDER: Your point is well taken; we recently discussed the question of arterial spasm secondary to venous stasis at one of these conferences. Dr. Edgar Allen has pointed out that ischemia and necrosis of the vessel wall may follow as a result of stasis; therefore, prompt treatment is doubly important. Dr. Smith, would you have advised embolectomy in this case?

DR. SMITH: I would have considered it but the lesion was difficult to localize and I thus would have been doubtful about advising it.

DR. ALEXANDER: How may the site of an embolus be localized?

DR. SMITH: The presence or absence of arterial pulsations at a given level, the distribution of pain and the line of demarcation of ischemia all must be considered in establishing the locale of an embolus. The histamine wheal test may also be helpful. Often, accurate localization is impossible.

DR. ROOS: Embolectomy is particularly difficult if the embolus lies in an artery above the inguinal ligament.

DR. ALEXANDER: This patient was given anticoagulants, heparin and dicumarol. Dr. Moore, what is the effect of these agents?

DR. C. V. MOORE: They are used to prevent further intravascular clot formation. They, of course, have no effect on the clot already formed except to prevent its further propagation.

DR. ALEXANDER: The prothrombin time fell to 33 per cent of normal. Is that the desired range?

DR. C. V. MOORE: We do not have well defined standards for comparison because we have been using a different method for prothrombin times from that which the Mayo Clinic has employed. We attempt to keep the prothrombin time between 10 and

30 per cent of normal so the value of 33 per cent would probably be satisfactory. I am not sure, however, how well figures from various clinics can be correlated. With our method, a prothrombin time of 10 to 30 per cent does represent marked hypoprothrombinemia.

DR. ALEXANDER: Would you comment on the danger entailed when the prothrombin time falls to low levels?

DR. C. V. MOORE: The occurrence of serious hemorrhage must be kept in mind.

DR. ALEXANDER: Does the coagulation time vary directly with the bleeding time?

DR. C. V. MOORE: No, nor does it vary too directly with the prothrombin time either. When the prothrombin time is low, one cannot be sure whether the coagulation time is prolonged; nevertheless, in spite of this fact, it is true that some patients who have low prothrombin times with normal coagulation and bleeding times do have serious hemorrhage. The exact explanation for this phenomenon is not clear.

DR. ALEXANDER: In instituting anticoagulant therapy, what is the method of choice?

DR. C. V. MOORE: This patient received what we consider the optimum regimen. Heparin was administered to cause immediate prolongation of the coagulation time and concomitantly dicumarol was given; an interval of twenty-four to forty-eight hours is usually necessary before the prothrombin time falls to adequate therapeutic levels and then heparin is discontinued.

DR. ALEXANDER: How is heparin best administered?

DR. C. V. MOORE: Probably the best method of giving heparin is by continuous intravenous infusion in 5 per cent glucose in water; our usual plan is to adjust the infusion, so that 25 to 30 mg. of heparin are introduced every hour; coagulation times are checked hourly by the capillary tube method. In our experience, this plan has been quite satisfactory.

DR. ALEXANDER: In summary, the discussion in this case has covered various aspects of this man's illness which lay in his cardiovascular system. It is believed that he most

likely had hypertensive cardiovascular disease and coronary artery sclerosis, probably with myocardial infarction. Subsequently, it seems likely that a mural thrombus formed in the left side of the heart, became detached and led to occlusion of the right femoral artery. Profound cardiac insufficiency complicated the clinical problem. Questions have been raised as to the possibility that rheumatic valvulitis was a major factor in the cardiac disease and thrombophlebitis has been mentioned as a possible cause of the peripheral vascular phenomena.

Clinical Diagnosis: Hypertensive cardiovascular disease; cardiac insufficiency; coronary artery sclerosis; myocardial infarction; mural thrombus and femoral artery embolism.

PATHOLOGIC DISCUSSION

DR. RICHARD D. JOHNSON: The significant gross findings were in the serous cavities, heart and in the lower extremities. The peritoneal cavity contained 1,000 cc. of yellow, clear fluid. There were 550 cc. of similar fluid in the right thorax, 100 cc. in the left thorax and 200 cc. in the pericardium.

The heart weighed 675 Gm. and all chambers were dilated. The left ventricle measured 15 mm. in thickness, the right 8 mm. The anterior descending branch of the left coronary artery was totally occluded by a grey thrombus. In the anterior wall of the left ventricle, extending from the apex to within 5.0 cm. of the base and involving the anterior portion of the interventricular septum, was an area of yellow and red, mottled, soft tissue in which no muscle bundles could be identified. Its cut surface retracted slightly. Attached to the overlying endocardium was a grey and brown friable thrombus.

Both lower extremities showed blue-black discoloration of the distal portions with clearcut lines of demarcation 12 to 14 cm. above the external malleoli. The discoloration was more intense in the right extremity with black shrivelled toes. There was a grey and red thrombus occluding the right pop-

lital artery and a red thrombus filling and distending the right femoral and iliac arteries. The arteries of the left leg were patent. No thrombi could be demonstrated in the major veins.

The kidneys weighed 200 and 180 Gm. respectively; their cortical surfaces were finely granular without significant reduction in the width of the cortex.

DR. ROBERT A. MOORE: On the basis of the gross findings, I think that we can answer the first question that Dr. Alexander proposed in regard to the nature of the heart disease. There was no evidence of rheumatic heart disease; furthermore, there was no abnormality of the aortic valve so that we may conclude that the patient did not have syphilitic heart disease. To the pathologist, there was definite inferential indication of hypertension as evidenced by cardiac enlargement without other evidence of heart disease and by the changes observed in the kidneys. There was sclerosis of the coronary arteries and other arteries of slight to moderate degree and complete occlusion of the left descending coronary artery. I assume from the discussion, Dr. Alexander, that one of the major points of interest to the clinicians is the time relation of the occurrence of the various lesions which were mentioned in the gross description. Let us turn to the microscopic slides in order to attempt to correlate the clinical features in this case. Figure 1 represents a section of the left descending coronary artery and one of its branches. The muscle wall is thin in some areas and the lumen is occupied by a mass which Dr. Johnson described as gray, firm and adherent and which retracted from the cut surface as a completely organized thrombus. Whatever thrombus was there was completely replaced by fibrous tissue through which recanalized channels pass. Thus, in the heart, 3 cm. from the origin of the left descending coronary artery, there is a completely organized lesion which is at least several months old. How much older than that cannot be determined anatomically for, as I have said here on other occasions, the anatomic or histologic age of lesions cannot

be determined past the time required for complete healing; there is no change thereafter. Let us next look at a section of the left ventricular wall in the region described by Dr. Johnson as being mottled, red and yellow with a thrombus lying over it. In Figure 2, a typical section is seen showing viable muscle at one point, collapsed muscle at another and necrotic muscle in a third area; in the latter region, the individual muscle fibers have lost their nuclei and their striations. Their cytoplasm consists of homogeneous or granular debris. Some of the muscle fibers have completely disappeared. We may therefore assume that the lesion had been present for a sufficient length of time that some of the dead muscle had been removed. That interval would be between three and seven days. Let us look at another region of the myocardium. (Fig. 3.) Here a different picture is seen. The dead muscle has been completely removed and there is nothing left but the outline of the fibrous tissue in between; note particularly that each one of the capillaries is visible. I think that a lesion of this type demonstrates more strikingly than any other means, except by the use of an injection mass, the rich capillary supply to the heart muscle. If one counts the number of capillaries and the number of muscle fibers in an injected preparation, as has been done, it is found that there are more capillaries than there are muscle fibers. In a section such as this when the muscle fibers have disappeared, the capillaries stand out in an extremely prominent fashion. Manifestly, from what I have said about the previous section this lesion is older for here all of the dead muscle has been removed. Thus, we may say that in the same general area of the myocardium, there is a lesion that is several weeks old, I would say from one to three weeks. Dr. Johnson described a thrombus on the endocardial surface of the ventricle in this region. Let us examine that area. In Figure 4, one sees muscle and probable Purkinje fibers which can be recognized by the extremely large and prominent myofibrillae; also, the ap-



FIG. 1. Section of the left descending coronary artery showing a completely organized thrombus. Several recanalized channels may be seen.

FIG. 2. Section of the left ventricular wall through the area of infarction. Note the area of necrotic muscle.

FIG. 3. Another area of myocardium through an area of older infarction. Note particularly the great number of capillaries.

FIG. 4. Section showing myocardium at the site of thrombus formation.

FIG. 5. Sections through the popliteal artery at the site of the embolus. Organization of the embolus is under way.

FIG. 6. Section of the kidney showing the changes of arteriolar nephrosclerosis.

parent vacuolation of the cells which actually represents the rich store of glycogen in the Purkinje fibers stands out in contrast to the contractile fibers of the heart. The thrombus is seen to be undergoing organization; there are capillary vessels extending out for a short distance and there is also

fibroblastic proliferation. The thrombus, in all probability, has been present for a period of several weeks, again probably one to three weeks. The rate of organization depends on so many different factors that I allow myself a good deal of leeway in estimating the age of the individual lesion.

In a section through the popliteal artery (Fig. 5), the internal elastic lamina, the muscular wall, the intima and the embolus contained in the lumen are all visible. At the junction of the intima and the thrombus, fibroblastic proliferation has begun; that is, the organization of the embolus is under way. I would estimate, on the basis of the very minimal degree of organization, that the embolus had occluded the lumen four to eight days before. In the femoral and iliac arteries, thrombus formation, secondary to the embolus in the popliteal artery, had occurred but there was no evidence of organization. That thrombus, therefore, had an age of one to three days.

Let us now consider the other lesions. In a characteristic section of the kidney (Fig. 6) several afferent arterioles can be seen. The glomerular vessels are tremendously thickened and their lumens are greatly decreased in thickness. There is, however, no necrosis in the walls. These sections, therefore, are an example of benign arteriolar nephrosclerosis rather than of malignant nephrosclerosis. The glomeruli show slight thickening of the basement membranes in some instances. Sections of the lungs showed numerous large macrophages containing abundant hemosiderin pigment in the alveoli, evidence of chronic passive congestion.

Now to return to a consideration of the case as a whole assuming that our estimates regarding the age of the various lesions are correct. As I have pointed out, they are reasonably correct as first approximations but, of course, there is much variation in the response of tissues in different individuals to injury or other pathologic changes. It seems likely to me that this patient suffered from hypertension for some time and this process led to the cardiac hypertrophy. During the discussion with Dr. Bottom regarding the

cardiac size I asked him if he would estimate the weight of the heart; he gave me the figure of 700 Gm. which certainly compares favorably with the actual weight of 675 Gm. I have seen Dr. Bottom estimate the size of hearts in radiographs frequently and he usually is just as reliable as our scales. Concomitant with hypertension, the patient had a moderate degree of sclerosis of the coronary arteries. Several months ago, one of the coronary arteries, the left anterior descending branch, was completely occluded but sufficient collateral circulation was present to prevent any immediate severe embarrassment and no infarct developed. Several weeks ago, for some reason not now apparent, small foci of infarction started to appear in the heart muscle. In association with the first infarct, a thrombus formed in the left ventricle and four to eight days before the patient's death a piece of that thrombus broke off and lodged in the popliteal artery to give rise to the terminal events.

Anatomic Diagnoses: Arteriosclerosis of the coronary arteries, slight; organized thrombus occluding the anterior descending branch of the left coronary artery; partially healed and recent infarcts of the anterior wall of the left ventricle and apex of the interventricular septum; mural thrombus in the left ventricle; partially organized thrombus in the right popliteal artery with partial occlusion; gangrene of the right ankle and foot and discoloration of the left ankle and foot; arteriolar nephrosclerosis; hypertrophy and dilatation of the heart (675 Gm.); congestion and edema of the lungs, advanced; chronic passive congestion of the liver, spleen and kidneys; hydropericardium (200 cc.); hydrothorax (left, 100 cc.; right, 550 cc.); ascites (1,000 cc.) and edema of the thoracic and abdominal walls, scrotum and the right lower extremity.

Book Reviews

The Essentials of Endocrinology. By Arthur Grollman. Second edition, 644 pp; 132 figures. Philadelphia, 1947. J. B. Lippincott Co. Price \$10.00.

Dr. Grollman has written a very lucid, clear and simple textbook. The disorders of the endocrine glands are discussed from the physiologic and clinical standpoints in straightforward language and with well chosen material. One does not require a large background of experience in this difficult field in order to understand the presentation. The illustrations are good; the clinical descriptions are adequate. One adverse criticism might be that there is a tendency to present a group of symptoms rather than to bring out their appearance in the course of a given disease.

The material of each chapter is accurate, although minor errors or omissions crop up. Thus, in the chapter on the parathyroids it is stated that the protein-bound blood calcium level is dependent on the total protein of the plasma rather than mainly on the albumin fraction. In the chapter on the thyroid gland, discussion is omitted of the physiology and pathologic physiology of exophthalmos and its possible relationship to the pituitary. In the chapter on the pituitary, emphasis is given to the work of Keller concerning the rôle of the different anatomical portions of the gland and the stalk, although this work has not been definitely confirmed. However, these criticisms are all minor and the book is highly recommended for the use of practitioner and student.

S. C. W.

Practical Physiological Chemistry. By Philip B. Hawk, PH.D., Bernard L. Oser, PH.D. and William H. Summerson, PH.D. 12th Edition. Pp. 1,323, with 329 illustrations and 5 color plates. Philadelphia, 1947. The Blakiston Company. Price \$10.00.

The twelfth edition of this well known

textbook and laboratory manual brings the subject matter up-to-date while preserving the time-tried plan of preceding editions. The text has been completely rewritten. New additions include sections on polarography, the theory and practice of photometric analysis, the Warburg tissue-slice technic, electrophoretic fractionation of plasma proteins, sulfonamides and antibiotics, composition of foods; and many new tests, experiments and quantitative procedures for blood and urine. Dr. Summerson, associate professor of biochemistry at Cornell University Medical College, appears as co-author for the first time in this edition and assumed a major rôle in the revision.

The text is divided into thirty-six chapters, the first seven introducing the physicochemical properties of solutions and the biochemical characteristics of carbohydrates, fats and proteins. Subsequent chapters deal with blood, urine and feces, the metabolic processes, and the various secretions and excretions of the body. Concise but sufficiently detailed laboratory experiments, tests and quantitative methods are given, each chapter concluding with a bibliography of selected references. An appendix furnishes details of preparation of reagents and solutions, together with tables listing the composition of foods and other useful data. Illustrations, graphs, tables and structural formulas are profusely scattered throughout the text. The paper is of good quality, the format is attractive, the typography is eminently readable, the volume is tastefully and sturdily bound and the index is adequate. Few typographical errors were noted.

The present edition assures the continued place of this book as a laboratory manual, teaching text and reference volume.

A. B. G.

Quantitative Clinical Chemistry. Interpretations. By John P. Peters, M.D. and Donald D. Van Slyke, PH.D., SC.D. Second edition, volume 1, pp. 1,041 with 62 figures, 40 tables. Baltimore, 1946. The Williams and Wilkins Company. Price \$7.00.

This is the initial volume of the second edition, completely rewritten and reset, of a classic work which first appeared in 1931 and set a new standard of scholarship in the field. The second edition, like the first, will be divided into separate volumes dealing successively with "Interpretations" and "Methods"; but such has been the growth of the subject that, in order to treat the material in the desired detail, it has been found necessary to subdivide "Interpretations" into two volumes, of which this is the first.

Volume I begins with an introductory consideration of what is termed energy metabolism, the over-all energy changes of the body, and then proceeds with a detailed consideration of the chemistry and metabolism of carbohydrates, lipids and proteins. The discussion of carbohydrates is divided into extensive sections on chemistry, physiology and clinical aspects. The comprehensive chapter on lipids is supplemented with sections on steroid hormones and fat-soluble vitamins. Part IV, dealing with protein metabolism, is subdivided into sections dealing successively with the net metabolism of proteins, the amino acids, urea, ammonia, creatin and creatinine, purines and pyrimidines. Each section is followed by a large bibliography, most containing over 200 selected references and one exceeding 700. Scattered throughout the text are numerous tables and figures, many illustrating the results of key investigations, others graphically or in tabular form summarizing metabolic pathways and other complex material. The paper is of good quality considering the exigencies of the times, the format and typography are agreeable, and the volume is attractively and sturdily bound and adequately indexed.

While entitled a clinical chemistry, the

exposition of this first volume is broader than is implied. The text properly deals at length with the biochemical and physiologic status of the normal subject, and this background is then integrated, so far as possible, with what is known of the changes observed in abnormal states. The treatment, moreover, gives sufficient historical perspective to indicate the chronologic development of ideas and thus attaches to the facts more meaning than would mere compilation. The whole makes a scholarly treatise, both in concept and accomplishment.

Dr. Peters indicates in his preface the difficulty in keeping the book abreast of expanding knowledge in so broad a field. Some of the chapters and bibliographies illustrate the difficulties involved.

A. B. G.

Penicillin: Its Practical Application. By various British authors under the editorship of Sir Alexander Fleming. Pp. 362 with 59 illustrations. Philadelphia, 1946. The Blakiston Company. Price \$7.00.

"Penicillin: Its Practical Application," a symposium on penicillin by more than twenty British authors, is an excellent review of most aspects of the topic. Under the editorship of Sir Alexander Fleming, who has written the chapters on History and Bacteriological Control himself, various British authorities have contributed articles on Manufacture and Chemistry, Pharmacology, and Methods of Administration. There are, as well, twenty chapters on the use of penicillin in the specific clinical conditions in which it has been found to be of value, including such topics as Chest Infections, Wounds and Gas Gangrene, Hand Infections, Obstetrics and Gynecology, Venereal Diseases and so forth. The emphasis throughout is on practical considerations and for this reason it should be particularly valuable to the practitioner and medical student who will find the material in no textbook and who would be completely snowed under by the huge literature on the

subject. The general principles governing the use of penicillin are very well covered, but of necessity a book of this size can neither cover the field entirely nor provide an inclusive bibliography. Most references are naturally to the British literature.

The book suffers somewhat from repetition, but this is unavoidable when contributors independently submit articles on closely allied topics. Though one might differ with occasional statements made by some of the authors, there is no question but that on the whole the discussions are authoritative and fairly complete.

Practical Malariology. Prepared under the Auspices of the Division of Medical Science of the National Research Council, by Paul F. Russell, M.D., H.P.H., Luther S. West, PH.D. and Reginald D. Manwell, SC.D. Cloth, 684 pages with 238 illustrations, 8 in color. Philadelphia, 1946. W. B. Saunders. Price \$8.00.

The practical aspects of malariology have been well presented by the authors, Russell,

West and Manwell. The senior author, especially, is well versed in the subject, having devoted his still active career exclusively to malaria, chiefly in the field. From the standpoint of need during the war, it was too bad that this text was not available sooner, as there were many who could have used the information to great advantage. On the other hand, the delay has been compensated for by the inclusion of much material discovered during the war.

The material is well arranged under six sections which include the parasite, mosquito, man, community, prophylaxis and control, and therapeutic malaria. Particularly noticeable is the outstanding selection of excellent photographic illustrations. Although somewhat sketchy in a few parts, the contents as a whole form an important contribution to the library of anyone interested in malariology.

L. T. C.

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